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CONSIDERATIONS IN THE PREPARATION AND USE OF POLIOMYELITIS VIRUS VACCINE

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In assessing the state of knowledge of any subject at a particular point in time, it is as important to define what is not known as it is to appreciate what is known. It is for this reason that I would like to discuss some of the problems still before us, with respect to vaccination against poliomyelitis, as well as to review knowledge gained in the course of recent work. "Can durable immunity be induced by a noninfectious poliomyelitis vaccine?" is one of the principal questions still to be answered. Since the ultimate answer to this question cannot be obtained until time has passed, we must content ourselves only with an examination of facts now known, from which we can make some tentative interpretations from the trends observed.

The hypothesis that the presence of neutralizing antibody in the circulating blood is an effective barrier in reducing the likelihood of paralysis by the poliomyelitis virus is now well supported by the great volume of indirect, as well as direct, evidence from studies in experimental animals and in man, on passive and active immunization.[1] In this discussion, therefore, I will examine the evidence that exists concerning the creation of antibody and also the persistence of antibody induced artificially by vaccination.[2] Observations in some, of many more, individuals who were vaccinated one and a half years earlier, and others vaccinated two and a half years earlier, will be shown. I will try to orient my remarks along practical lines but will do so principally by reference to the theoretical and experimental considerations upon which are based the preparation and use of poliomyelitis vaccine.

To begin a discussion such as this, from the practical viewpoint, it would be well to consider first the special attributes required of a poliomyelitis vaccine, as compared to vaccine for any other diseases, since a vaccine for poliomyelitis requires particular attention as regards both safety and effectiveness. We know only too well the uniqueness of paralytic poliomyelitis, among all of the infectious diseases; the unusual combination that exists here is the terror and tragedy inflicted to a degree that is out of all proportion to the frequency of attack. The relative infrequency of severe paralysis under natural circumstances requires, above all else, that the vaccine must be free, insofar as it is possible to create such a preparation, of the capacity to induce the disease that it is intended to prevent; nor should a vaccine for poliomyelitis cause such side-effects as would make its use undesirable. If either the direct effects associated with its use, or incidental side-effects to any constituent, are of such nature as to make one prefer the chance of escaping the paralytic disease, one would not have a practically useful immunizing agent.

PRINCIPLES OF VACCINE PREPARATION AND SAFETY TESTING

First, I would like to describe the principles upon which the preparation of poliomyelitis vaccine is based and, particularly, the considerations involved in testing

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Many of the experimental and theoretical considerations discussed in this paper are being elaborated in more detail for publication elsewhere.

This study was aided by a grant from the National Foundation for Infantile Paralysis.

1. Morgan, I. M.: Level of Serum Antibody Associated with Intracerebral Immunity in Monkeys Vaccinated with Lansing Poliomyelitis Virus, J. Immunol. **62**: 301, 1949. Bodian, D.: Sites of Immune Barriers in Poliomyelitis, in Hartman, F. W.; Horsfall, F. L., Jr., and Kidd, J. G.: The Dynamics of Virus and Rickettsial Infections, New York, Blakiston Company, 1954; Experimental Studies on Passive Immunization Against Poliomyelitis: I. Protection with Human Gamma Globulin Against Intramuscular Inoculation, and Combined Passive and Active Immunization, Am. J. Hyg. **54**: 132, 1951. Hammon, W. McD.; Coriell, L. L., and Wehrle, P. F.: Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis: 4. Final Report of Results Based on Clinical Diagnosis, J. A. M.A. **151**: 1272 (April 11) 1953. Howe, H. A.: Studies of Active Immunogenesis in Poliomyelitis: I. Persistence and Recall by Homotypic or Heterotypic Superinfection of Neutralizing Antibody Originally Induced in Chimpanzees by Vaccination or Infection, Am. J. Hyg. **60**: 371, 1954; II. Lack of Immunity in Chimpanzees Receiving Formol-Inactivated Vaccines of Marginal Antigenic Potency, ibid. **60**: 392, 1954. Koprowski, H.: Practical Application of Living Virus Vaccines, in Hartman, F. W.; Horsfall, F. L., Jr., and Kidd, J. G.: The Dynamics of Virus and Rickettsial Infections, New York, Blakiston Company, 1954.

2. Salk, J. E., and others: Studies in Human Subjects on Active Immunization Against Poliomyelitis: I. A Preliminary Report of Experiments in Progress, J. A. M. A. **151**: 1081 (March 28) 1953. Salk, J. E.: Recent Studies on Immunization Against Poliomyelitis, Pediatrics **12**: 471, 1953. Salk, J. E., and others: Studies in Human Subjects on Active Immunization Against Poliomyelitis: II. A Practical Means for Inducing and Maintaining Antibody Formation, Am. J. Pub. Health **44**: 994, 1954. Salk, J. E.: Present Status of the Problem of Vaccination Against Poliomyelitis, ibid. **45**: 285, 1955.

for safety. The objective in the preparation of a poliomyelitis vaccine cannot include the knowing or willful acceptance of a risk that is tangible, or measurable to any degree. Any risk that is involved, so long as it is recognized, must be corrected, whatever may be its cause; in the preparation of experimental vaccines in

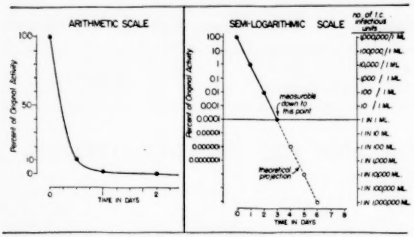

Fig. 1.—Rate of destruction of poliomyelitis virus infectivity at 37 C in presence of 1:4,000 formaldehyde solution (Formalin) at pH 7.

our own laboratory, and on a larger scale for field trial, it was the factor of safety, above all else, that imposed the limitations in the rapidity with which our studies were progressively advanced. To permit the practical application in the field to come close upon the heels of the rapid advances that were being made by investigations in the applied aspects of the problem, rather extensive transformation and expansion of the various facilities necessary for the availability of vaccine was required.

Although there were no indications either from our own studies in some 15,000 children, or from the much larger experience in the field tests of 1954, that the vaccine preparations employed contained infectious virus, it is understood now generally that certain lots of vaccine used in April, 1955, were associated with the subsequent development of paralytic poliomyelitis. This demanded a very intensive reexamination of the theoretical and practical implications of vaccine preparation, testing, and use.

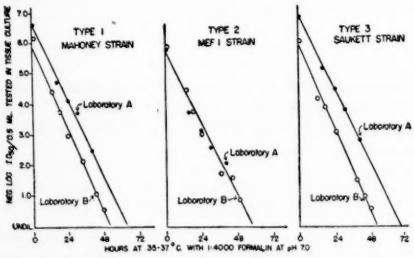

Fig. 2.—Composite of data on rates of destruction of infectivity of types 1, 2, and 3 virus for 13 lots of vaccine prepared by one manufacturer and 20 lots prepared by another. Points indicate mean of virus titers at intervals after addition of formaldehyde solution (Formalin) to warmed fluids.

I might say at this point that my own evaluation of the recent reexamination of the manufacturing and testing processes suggested a need for adjusting the techniques employed for large-scale operations so as to approximate that which it was possible to accomplish on an experimental basis; the objective is to yield the consistently satisfactory preparations that it has been possible to achieve, not only in the laboratory but even on a large scale. The theoretical considerations that applied originally are still sound and applicable—what is required is closer approximation in practice. I would like to discuss the theoretical considerations first and then to show how the practical problems have been, and are being, met.

It has been realized always that the preparation of a safe poliomyelitis vaccine would, at the beginning at least, require adherence to detail such as is not demanded for the preparation of any other immunizing agent. It was recognized, too, that there must be incorporated into the vaccine preparation process itself a test for safety, which we refer to as "the margin of safety," of such degree that the most sensitive tests upon a sample of each successive batch would be negative for living

Experience of Two Laboratories in Preparation of Vaccine for Field Trial on Production Scale

Sequence	Laboratory A *	Laboratory B
1	—	—
2	+	+
3	+	+
4	+	—
5	+	+
6	+	+
7	+	+
8	+	+
9	+	+
10	+	+
11	+	+
12	+	+
13	+	+
14	..	+
15	..	+
16	..	+
17	..	+
18	..	+
19	..	+
20	..	+

* Symbols indicate whether finished vaccine met all criteria for safety: — = no, + = yes.

virus unless something unexpected had occurred, unknowingly, in the process of manufacture, or in subsequent handling, or in testing; it would follow that such would not be expected to occur but rarely. To help in knowing where the difficulty might have occurred in any given instance, tests are needed at various steps in processing, including the final stages. A series of observations, both in our laboratory and in the laboratories of manufacturers of biologicals, indicated that the desirable objective of consistency in reproducibility of vaccine preparation with an adequate margin of safety could be achieved.

In the early phases of our investigations it was necessary, in exploratory experiments, to determine the nature of the reaction between formaldehyde and poliomyelitis virus,[3] using various concentrations of formaldehyde, different temperatures, and different degrees of acidity. The conditions selected for preparation of field test vaccine were those that would lend themselves most readily to large-scale adaptation in a way that would provide the desired margin of safety not only with respect to the

3. Salk, J. E., and others: Formaldehyde Treatment and Safety Testing of Experimental Poliomyelitis Vaccines, Am. J. Pub. Health 44:563, 1954.

destruction of virus infectivity but also with respect to the retention of antigenicity. Such studies furnished the principles upon which a carefully controlled inactivation process could be developed for use in the laboratories of any producer of biological products that could acquire the staff and facilities for making poliomyelitis vaccine.

I can best illustrate what I mean using the accompanying figures, which show the generally expected behavior, based upon experience with experimentally produced vaccine. The left-hand portion of figure 1 shows that within the first 12 hours after the beginning of chemical treatment, 90% of virus infectivity is destroyed; within the subsequent 12 hour period, 90% of the infectivity that still remains is destroyed—or, about 99% of virus infectivity is eliminated within the first 24 hour period; in 48 hours, approximately 99.9% of the original infectious activity is obliterated. To eliminate the last traces of infectivity to a point below which none can be detected requires continuation of treatment for a number of days longer. From the practical viewpoint, the question that had to be answered was, "At what point may it be presumed that virus infectivity is destroyed, either totally or, at least, to a degree beyond which it can no longer be measured and, therefore, can be presumed not to be

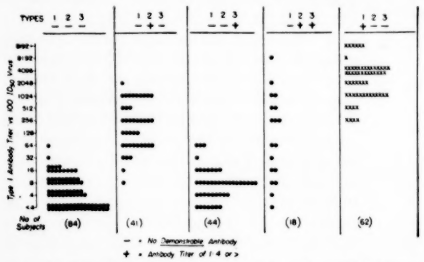

Fig. 3.—Type 1 antibody response to first dose of vaccine in persons with different prevaccination antibody patterns (vaccine lot 309). Different prevaccination antibody patterns are indicated at the top of each column.

harmful to man?" The right-hand portion of figure 1 illustrates further the data depicted on the left, but in another way—that is to say—on a semilogarithmic scale, which allows a more precise examination of the portion of the left-hand curve that is in the range below 1% of remaining infectivity. Here it may be seen that in the course of three days the infectivity for tissue culture of material being converted into vaccine has been so altered that, whereas originally it contained one million tissue culture infectious units per milliliter, at the end of the first three-day period, there remained but one tissue culture infecting unit per milliliter. If treatment is continued for not less than an additional six days, it is expected that with thorough mixing of virus and formaldehyde, the maintenance of uniform temperature, a reasonably homogeneous population and adequate dispersion, the material treated for a total of nine days or longer should, theoretically, be free of any demonstrable virus—even if all of the fluid being converted into vaccine were tested in tissue culture or even in man. Such experiments were done under the conditions that apply not only in our laboratory but on a large scale in other laboratories in this country and abroad (fig. 2 and table).

The critical factors that influence the slope of the line in the right-hand portion of figure 1 are (1) temperature, (2) formaldehyde concentration, and (3) pH. Since the amount of free formaldehyde will be influenced by such

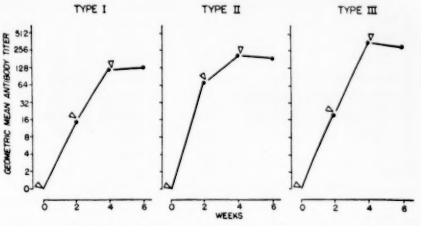

Fig. 4.—Geometric mean titers after each of three doses of reference vaccine "A," 1 ml. given intramuscularly to 20 subjects with no pre-antibody to any type.

constituents as the protein content, or the concentration of free amino acids, then constancy of composition of the fluid being converted into vaccine is a factor that would affect the rate of reaction. In spite of our ability to control these variables within practicable limits, it is still necessary to ascertain, by suitable tests, that all of the considerations have, in fact, been properly effected. There is one critically important factor that demands

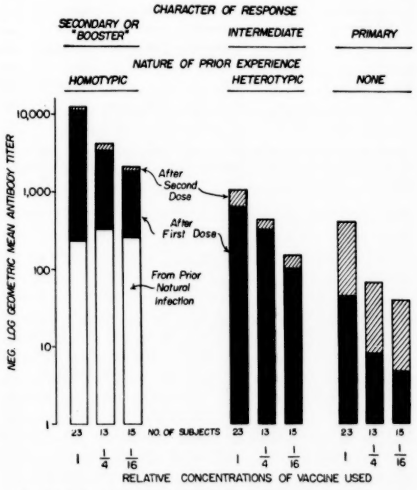

Fig. 5.—Different patterns of antibody response, depending on nature of prior immunologic experience, after two doses of reference vaccine "A" given two weeks apart, with blood drawn two weeks after each dose.

close attention and that is the matter of uniform mixing; another is the use of such techniques that reduce, if not eliminate, risk of recontamination with live virus. Failure to mix adequately will introduce such uncontrollable variables as may be described by the term "fractional

inactivation," and this may make it appear that resistant particles are present. Another factor is the use of filtration procedures to remove particles that might interfere with inactivation. As has already been mentioned, a check for any deviation from the expected is made by tests upon suitable samples removed at particular stages in the course of processing.

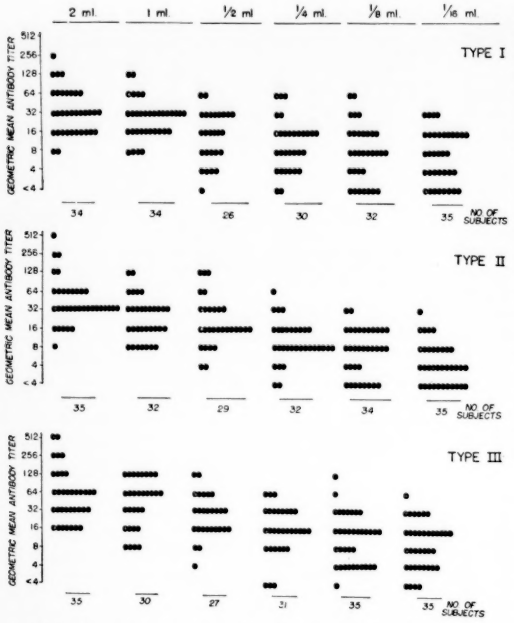

Fig. 6.—Dosage effect: Type 1, 2, and 3 antibody response two weeks after one dose of reference vaccine "A" given intramuscularly to subjects with no demonstrable preantibody to any type.

In the critical review that was made recently of the requirement for manufacture, tests were specified at two additional check points in the process, and the volumes of fluid to be tested at each step for each batch were set at fixed quantities. In addition, failure of a batch to be inactivated in the expected time would preclude its being reprocessed, and it is required that such batches be discarded. This is merely in conformity with the present requirement that there be demonstrated an adequate margin of safety for each batch of vaccine. The details that have been spelled out merely define what is meant by adequate margin of safety and in actual practice are further reinforced by requesting compliance with the original requirement that there be satisfactory consecutive experience of each manufacturer in being able to produce vaccine consistently free of living virus, and with the desired margin of safety.

It may be said that the design of the inactivation process, for the experimentally produced vaccine and for larger scale preparations, was intended to provide a quantitative expression of margin of safety. This was based upon the opinion that the testing merely of a sample of the final preparation, as is customarily employed for most biologicals, was inadequate for the special needs of the vaccine under consideration.

But there are still many other technical aspects of the broad problem upon which investigations will continue for a long time to come. One of these is in regard to the particular strains of virus for the most effective vaccine. The strains selected for our very first studies were chosen because, among many from which selections were made, these produced the highest infectivity titers in tissue culture and were also shown to be highly antigenic in monkeys and man. It has now been found that, within broad limits, high infectivity and high antigenic potency are not necessarily associated, and, in fact, they are independent properties. These trends emerge from a series of investigations in which strains are being selected that are among the most potent antigenically, and from among these we will select those that are of low pathogenicity for monkeys when administered by peripheral routes. The principle objective of this phase of our studies is to incorporate in the vaccine a type 1 strain that has the same attributes of high antigenic potency as do the MEF-1 strain of type 2 virus and the Saukett strain of type 3, that appear to be more potent antigenically than does the Mahoney type 1 strain; and while doing so, to select one of low peripheral pathogenicity for monkeys. But the latter is only a secondary consideration, since the first requirement that must be satisfied regardless of strain is that it be rendered noninfectious for man. In studies with laboratory-selected variants that are avirulent, some are very poor antigens whether they are used in their fully infectious form or after inactivation with formaldehyde solution (Formalin). This is something of considerable theoretical and practical interest.

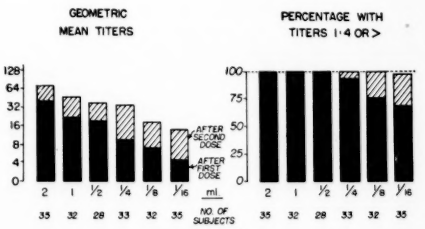

Fig. 7.—Type 2 antibody response two weeks after two doses of reference vaccine "A" given two weeks apart.

IMMUNOLOGIC FACTORS INFLUENCING VACCINE EFFECTIVENESS

The question of vaccine effectiveness is, of course, secondary to the question of vaccine safety. I would, therefore, like to discuss now the question of vaccine ef-

fectiveness. Here we have two distinct issues: (1) the immediate one—the immune response that can be expected after each of the three doses of vaccine, and (2) one that arises later—regarding the degree of persistence of immunity after the third inoculation. There is the further question of the spacing and frequency, if later inoculations are required.

Primary Vaccine Response.—The various factors that influence the primary response to vaccine are illustrated in a series of figures to follow. The first point that I wish to make is that antibody response is influenced by prior immunologic experience. For example, an individual who has not had any prior poliomyelitis virus infection reacts quite differently to vaccination than does an individual who has had an infection with one or more of these viruses. This is illustrated in figure 3, where it may be seen that the antibody response to the first dose of a relatively poor vaccine was quite different in persons who had no previous immunologic experience as compared with those who had a prior infection with either type 2 or type 3 virus, or both; it is to be expected, of course, that there will be a very different pattern of reactivity if there has been a prior homotypic infection, i. e., type 1 in this instance. It should be clear from these data that, from a practical point of view, it is necessary to know the nature of the antigenic response in persons who have had no prior immunologic experience if one is to make valid comparisons concerning the nature of the influence of vaccine potency, time, and spacing of inoculations, and any other questions that can be answered only by the application of quantitative immunologic methods. It is for this reason that I will confine this presentation, except as necessary, to make a particular point, to data derived in studies in children who had not had any prior experience with any of the poliomyelitis viruses.

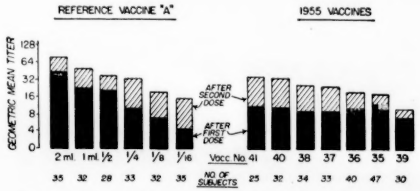

Fig. 9.—Comparison of seven lots of 1955 vaccine with reference vaccine "A." Type 2 response two weeks after two doses given two weeks apart.

Figure 4 illustrates the degree of antibody response after three doses of vaccine given to a group of children who prior to vaccination had no antibody to any of the three types. It is clear from this chart that a substantial response occurred after the first dose of vaccine, a moderate increase occurred after the second dose, but little or no increase occurred after the third dose when the three doses of vaccine, of the potency used here, were spaced with an interval of two weeks between each. The reason for the suggestion that the third dose should be postponed is indicated by these data, and the reason for the suggestion that an interval of seven months or more be used will be shown by the results of other experiments referred to later in this discussion.

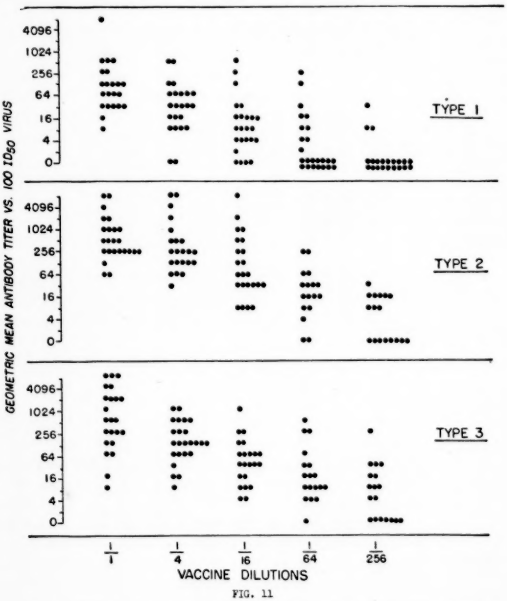

FIG. 11

Fig. 8.—Antibody response in groups of monkeys vaccinated with diminishing dilutions of reference vaccine "A" given in three doses intramuscularly, 1 ml. each week one week apart, with blood drawn one week after third dose.

Additional evidence showing the influence of two other factors; namely, vaccine potency and time for producing the full immunologic effect, superimposed upon the influence of the particular kind of prior immunologic experience, is illustrated in figure 5. This summary reveals that vaccines differing in potency in fourfold and sixteenfold steps elicit different degrees of antibody response. Moreover, a second dose produces substantially more antibody in persons who have had no prior immunologic experience as compared with persons who have had a prior heterotypic experience, or in persons who have had a prior homotypic experience. After the lapse of a suitable period of time after the primary and intermediate types of response, a later inoculation will then evoke titers to levels observed for the booster-type response (fig. 5). But, it is clear that the potency of the vaccine influences the degree of response regardless of the nature of the prior immunologic experience.

So as not to complicate these matters unduly, I would like to mention that the foregoing charts have indicated that persons with no antibody to any of the three types are the ones with whom we need be concerned chiefly;

two doses of vaccine, with spacing two weeks or longer, appears to be the most efficient way to administer vaccine for the relatively limited effect that can be induced in the primary stage. Moreover, it is clear that this primary effect is influenced by the potency of the vaccine used. Figure 6 shows in somewhat more detail the influence of vaccine potency in effecting a change in antibody status in groups of individuals who had no detectable antibody prior to vaccination. It is clear that when the dose given intramuscularly is varied from 2 ml. to 0.06 ml. that there is a spread in the difference in the frequency with which antibody appears and also variation in the degree of the average response. Thus, with a potent vaccine it is possible to induce the formation of antibody in all of groups of the sizes indicated, and with weaker vaccines proportionately lesser effects are induced. The data for type 2 are illustrated in figure 7 in a somewhat different fashion, showing the geometric mean antibody level after the first and after the second dose of vaccine; in addition there is shown the percentage of individuals who had no antibody to any type before vaccination but, as a result of vaccination, developed a distinctly measurable amount of antibody; comparisons are shown after the first and second dose.

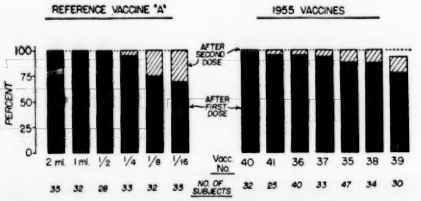
REFERENCE VACCINE "A"
1955 VACCINES
PERCENT
AFTER SECOND DOSE
AFTER FIRST DOSE
2 ml. 1 ml. ½ ¼ ⅛ 1/16
Vacc No. 40 41 36 37 35 38 39
NO. OF SUBJECTS 35 32 28 33 32 35 32 25 40 33 47 34 30

Fig. 10.—Comparison of seven lots of 1955 vaccine with reference vaccine "A." Type 2 response, showing percentage of subjects with demonstrable antibody (1:4 or more) two weeks after each of two doses given two weeks apart.

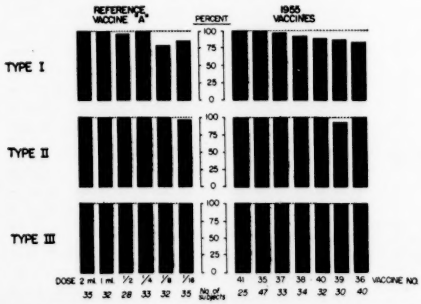
REFERENCE VACCINE "A"
PERCENT
1955 VACCINES
TYPE I
TYPE II
TYPE III
DOSE 2 ml. 1 ml. ½ ¼ ⅛ 1/16
VACCINE NO. 41 35 37 38 40 39 36
NO. OF SUBJECTS 35 32 28 33 32 35 25 47 33 34 32 30 40

Fig. 11.—Comparison of seven lots of 1955 vaccine with reference vaccine "A," showing percentage of subjects with demonstrable antibody (1:4 or more) two weeks after two doses given two weeks apart.

The data in the foregoing figures were derived in the course of experiments designed to help establish the significance for man of a laboratory test for potency as performed in experimental animals. By varying the dose of reference vaccine "A," in studies both in man (fig. 6) and in laboratory animals (fig. 8), it then becomes possible to establish a basis for the significance of any laboratory test, whether it be done in monkeys, mice, guinea pigs, or any other animal. The underlying principle is the use of a standard reference vaccine for measuring potency in comparison with the unknown to be approved for use in man. To help further in this correlation, a group of seven batches of vaccine, prepared for use in 1955, was also tested in the same way, and the relative activity of these vaccines in children was compared with that of the different quantities of reference vaccine "A." The relative potency of the type 2 component of the commercially prepared material, expressed in terms of geometric mean titer of antibody, is shown in figure 9 and in terms of percentage of individuals who showed a response after the first and after the second dose (fig. 10). Similar data are shown in figure 11 for all three types, in comparison with different quantities of reference vaccine "A."

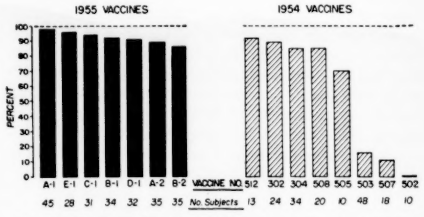

Fig. 12.—Percentage of children with no prior demonstrable antibody to any type who had a type 1 antibody response on the 14th day after first dose of vaccine.

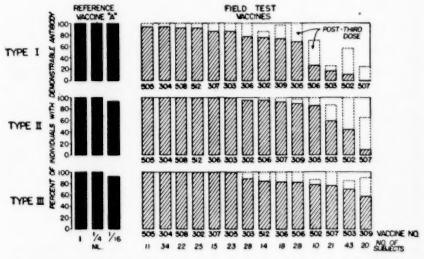
REFERENCE VACCINE "A"
FIELD TEST VACCINES
POST-THIRD DOSE
PERCENT OF INDIVIDUALS WITH DEMONSTRABLE ANTIBODY
TYPE I
TYPE II
TYPE III
505 304 508 512 307 303 304 302 309 305 506 503 502 507
1 ¼ 1/16 ML.
VACCINE NO.
11 34 22 25 15 23 29 14 18 28 10 21 43 20
NO. OF SUBJECTS

Fig. 13.—Antibody response in human subjects with no antibody for any type prior to vaccination, showing percentage of subjects with demonstrable antibody after two doses given two weeks apart (1954 field trial vaccines).

By means of such quantitative immunologic studies it is now possible, on the basis of a laboratory test performed in any of a variety of ways and in any of a number of animal systems, to predict the probable performance of any vaccine applied in human subjects so long as the vaccine in question is so constituted, and stored, that it will not deteriorate between the time of testing and the time of use. You will recall that in the vaccines prepared a year ago it has been established that the thimerosal (Merthiolate), or a decomposition product thereof, had an adverse effect upon the antigenicity, and particularly upon the type 1 component. The evidence

V 15
1955

suggests that this factor measurably influenced the response to the vaccines used in the 1954 field studies. This has been corrected by either (1) the elimination of a preservative, or (2) the use of thimerosal with edathamil (ethylenediaminetetraacetic acid), which tends to stabilize the thimerosal, or (3) the use of other preservatives. Any of the preservatives accepted for use must be shown to have no adverse effect upon the stability of the vaccine. That the vaccines used in the field trial were,[4] for the most part, less potent than those now available, is illustrated in figures 12 and 13. Figure 14 illustrates the difference in performance of vaccine with and without thimerosal, and of vaccine with thimerosal and edathamil, as compared with vaccine with no preservative.

Antibody Response to Vaccine Administered by Different Routes.—There have been a number of questions concerning antibody response to vaccine given by different routes. I would like to show, in figure 15, the data that are available on antibody response to vaccine given subcutaneously, intramuscularly, and intradermally. It is clear that 1 ml. of vaccine given intramuscularly or subcutaneously elicits about the same order of response; however, there seems always to be a slight advantage, as measured by mean antibody level, following intramuscular injection. When different quantities of vaccine given intramuscularly are compared with 0.1 ml. given intradermally, it would appear that the latter is about equal in effectiveness to 0.25 ml. given intramuscularly. Thus 0.1 ml. intradermally is not as effective, in inducing antibody formation, as is 1 ml. intramuscularly; but, it does appear that this small dose, given intradermally, is somewhat more efficient than a corresponding amount given intramuscularly.

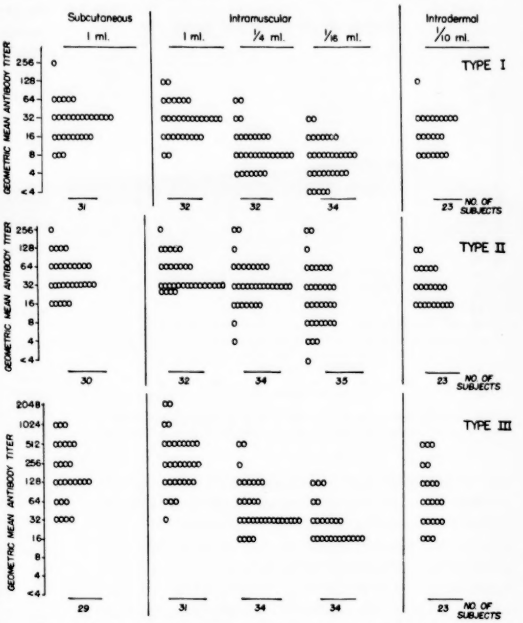

Fig. 15.—Type 1, 2, and 3 antibody response to reference vaccine "A" two weeks after two doses given two weeks apart by different routes of inoculation.

Optimal Conditions for Eliciting the Booster Effect.—In the course of our earliest investigations, it became apparent that in man frequent multiple inoculations, given over a period of a few weeks, were an inefficient way of administering vaccine. It was apparent, furthermore, that the longer the interval between inoculations the better the effect. This total experience has indicated that 1 ml. of vaccine of reasonable potency, given to subjects who have no antidoby to any of the three types, will induce antibody formation in the majority, and a second dose, given two weeks or longer thereafter, will add to this effect; if a number of months is allowed to elapse, the advantage of the third dose will be increased as the time is prolonged, up to approximately seven months, or later, at which time it appears that the height of the hyperreactive state is reached. The evidence indicating the advantage of the relatively long interval between the second and third dose is shown in figure 16, which summarizes data from an experiment in which a sample of vaccine was used that, over the six month period of the study, was deteriorating because of the influence of thimerosal. In spite of this, the advantage of time is evident, but the full effect of the third dose that would have been elicited, had a more potent vaccine been used, is not clear from the mean antibody titers observed. Nevertheless, the trend in favor of the longer interval is evident.

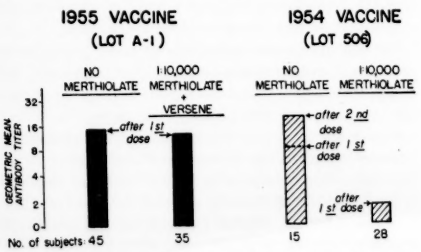

Fig. 14.—Type 1 response to 1955 vaccine (lot A-1) and 1954 vaccine (lot 506). In this instance Versene refers to edathamil (ethylenediaminetetraacetic acid).

The influence of a more potent vaccine, when used for booster, superimposed upon a more adequate primary stimulus, is shown in figure 17. The degree of response during the primary phase, following the use of

4. Salk, J. E., and others: Antigenic Activity of Poliomyelitis Vaccines Undergoing Field Test, Am. J. Pub. Health 45: 151, 1955. Salk, J. E.: Vaccination Against Paralytic Poliomyelitis: Performance and Prospects, ibid. 45: 575, 1955.

vaccine lots 303 and 507 is illustrated, as well as the degree of decline during the 10 months that followed; and then the degree of antibody response to the booster is also shown, along with the control representing the response of previously uninoculated children. Persons who initially had vaccine lot 303, and were then given

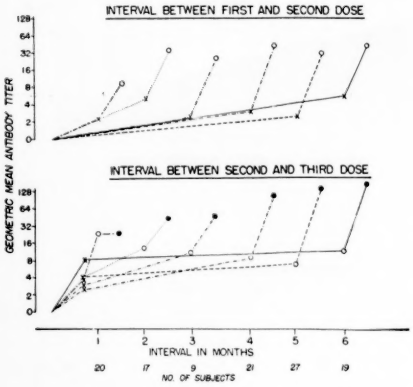
INTERVAL BETWEEN FIRST AND SECOND DOSE
INTERVAL BETWEEN SECOND AND THIRD DOSE
GEOMETRIC MEAN ANTIBODY TITER
INTERVAL IN MONTHS
NO. OF SUBJECTS
20 17 9 21 27 19

Fig. 16.—Influence of time intervals on type 2 response to second or third doses of vaccine (lot 309) in human subjects with no demonstrable preantibody to any type.

one of the other commercial vaccines for the booster, exhibited marked rises in antibody to all three types. By comparison, individuals who had received primarily vaccine lot 507 experienced no booster effect to the type 1 component, a rather poor response to type 2, and a more adequate type 3 response. It is clearly evident that there must be a reasonably substantial primary effect for a full secondary, or booster, response. Other data bearing on the question of booster response, when the secondary

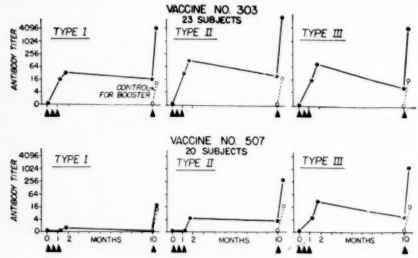

Fig. 17.—Effect of booster dose 10 months after vaccination with two different vaccine lots used in 1954 field trials.

stimulation is given seven months or longer after the primary, are shown in the next several figures. Here may be seen, in some instances, that even though little or no primary response was elicited, there appears to have been some sensitizing influence as evidenced by the hyperreactive response at the time of the booster.

The general pattern of response, as may be seen in these data, seems to be one in which there is a somewhat more rapid decline in the early postvaccination period followed by a more gradual decline or by a plateau, which suggests that antibody persistence following a course of vaccination of the kind here employed could be expected to persist for a number of years. Figure 18 summarizes observations in 14 individuals who, with exceptions, as noted at the different intervals, were followed for a period of one and one-half years. At that time a fourth inoculation was given to determine the character of the response that would be elicited. It is clear that the decline that occurred in the preceding year was replenished, and then exceeded to a slight degree by the second booster. These individuals will be followed to determine whether or not the rate of decline of antibody following the second booster is the same or, perhaps, more gradual than after the first. However, the magnitude of the level of antibody maintained during the year after the first booster, and the level achieved after the second is considerable, indeed. Several individual ex-

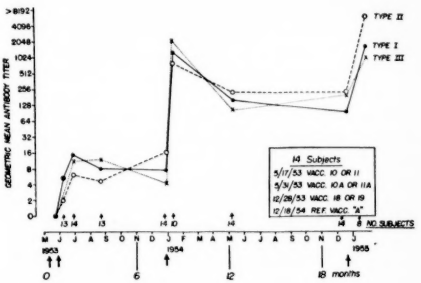

Fig. 18.—Antibody persistence after primary and secondary antigenic stimulation in children with no preantibody to any type who were observed over one and one-half years.

amples of persistence after primary, and of booster response, are shown in figures 19 and 20. It is to be noted that vaccine lot 503 was a relatively poor vaccine in comparison with the others used for boosters.

To provide further indications of trend in regard to persistence, data are presented in two individuals, of many, from whom blood samples have been tested two and one-half years after primary vaccination. These persons received 0.1 ml. intradermally of each of three virus types on two occasions, in August or September of 1952, and were then reinoculated almost two and one-half years later. The indications are that the relatively low levels of antibody, elicited by the primary immunizing procedure, tended to persist, and when a booster dose was given, even as long as two and one-half years later, a very sharp response was observed. The degree of persistence following the booster is now being followed. These examples of two and one-half year persistence are in persons who had antibody for only one type prior to first vaccination (fig. 21).

Antibody Response to Vaccination and Infection.—As a matter of interest, let us compare the levels of antibody observed in vaccinated individuals with those observed in persons who have experienced natural infection. To illustrate this point, figure 22 shows the prevaccination and postvaccination antibody titers of a group of 61 individuals, for whom we had such data, from among those who had received their initial inoculations with vaccines lot 303, 305, 306, or 512. In the prebooster period, the type 1 antibody levels of all individuals were below 1:32; 14 days after the booster they all had levels beyond this range, with a high proportion clustering at the level of 1:8,000+. For comparison, there is charted the levels of antibody observed in a group of 56 persons with type 1 paralytic poliomyelitis, and from whom serial bleedings were obtained at approximately weekly intervals while they were hospitalized. The geometric mean level of antibody was 1:128 at the time of hospital admission and shortly after onset of paralysis; there was no serologic evidence

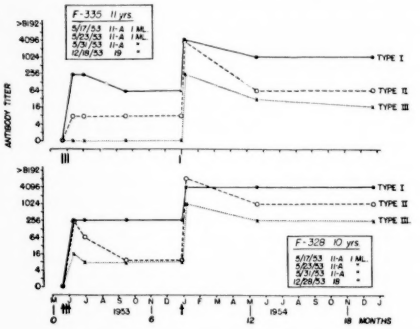

Fig. 19.—Antibody persistence after primary and secondary antigenic stimulation in two children with no preantibody to any type.

of prior infection with any other virus type. The antibody measurement recorded in this figure was the highest observed in the series for each individual; the geometric mean level of the highest titers was slightly less than 1:1024. From other experiences, it is to be expected that these high titers will decline over a period of time and will stabilize at a mean level of approximately 1:128.

It is evident from these data that there occurred, as a result of an infection with paralytic consequences, levels of antibody that in general were higher than that induced by primary vaccination with a killed-virus vaccine. However, it was equally clear that the level of antibody induced with a killed-virus vaccine, when a booster dose was given at a suitable interval, was higher than that induced by the infectious process.

In the right-hand portion of figure 22 are data from another group that is of interest. These data are from a study of 27 children who had been vaccinated either in the spring of 1953 or the spring of 1954, and, in the course of follow-up bleedings, in the winter of 1953 or 1954, respectively, it was evident that these children had experienced a natural infection. This was indicated by the sharp difference in the level of antibody for one type only, when the early and late postvaccination blood

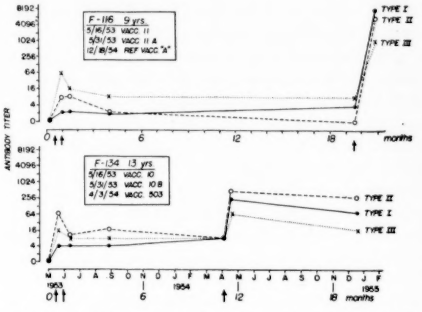

Fig. 20.—Antibody persistence after primary and secondary antigenic stimulation in two children with no preantibody to any type who were observed over one and one-half years.

samples were compared. In this group of 27 are 2 children who had a type 3 infection, diagnosed serologically; 12 had type 1 infections; 13 had type 2 infections. It is clear that the level of antibody observed in these subjects was, in general, higher than that observed in paralyzed convalescents. It is as if infection, in a previously vaccinated person, elicits a booster-type antibody response corresponding to the infecting type.

There is a similarity between the levels of antibody following a booster injection, and the postinfection levels in previously vaccinated individuals. The distribution of

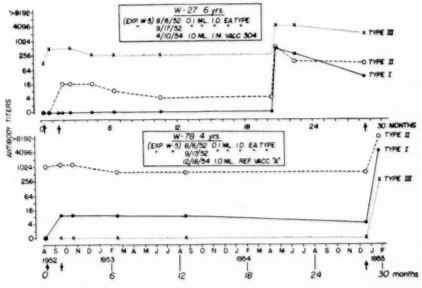

Fig. 21.—Observations over two and one-half years in two children of first group inoculated.

levels in each appear to be higher than that observed in recently paralyzed convalescents. It would seem from these data, therefore, that the assertion that the levels of antibody following the use of a killed-virus vaccine are lower than those observed in persons who have been infected is, indeed, true. But this is only part of the truth.

The whole truth indicates that the level of antibody induced by a properly prepared killed-virus vaccine, properly used, can be higher than that level induced by infection.

COMMENT

It should be clear from all that has been presented that the objective of the immunization process is to effect an immunologic response that will last for a considerable period of time. It appears that this can be accomplished by the introduction of an adequate antigenic mass, the influence of which will be evident after each of the three inoculations. The height of the antibody titer induced by the primary vaccinating doses (two doses spaced two to four weeks apart) is influenced by the intensity of the primary stimulus; i. e., dosage and potency of the vaccine. The height of the antibody titer after the booster dose is influenced by the length of the interval between the primary and secondary injections and by the size and potency of the booster dose. The level of antibody present at any given time after vaccination varies among individuals but is influenced by the total prior immunologic experience as well as by the interval that has elapsed after vaccination. The rate of decline from the different levels achieved after primary and booster doses has been described and in general appears to be more rapid shortly after the postinoculation level; this is followed by a plateau or a very gradual decline. In addition to these effects that are measurable directly, there appears to persist a state of heightened immunologic reactivity that is evident upon reinoculation or upon exposure. This state of hyperreactivity probably does not decline with time. Because of it, antibody levels may be further enhanced by revaccination, if need be, or will be augmented in the course of natural exposure.

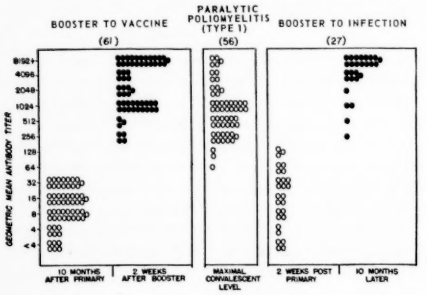

Fig. 22.—Comparison of antibody response to vaccination and to infection.

Although we have said that the ultimate objective of these investigations is to provide the basis for the preparation and the use of a safe and effective vaccine against paralytic poliomyelitis, the orientation of our studies at this time is to determine the degree of completeness with which effectiveness can be demonstrated—first, by means of blood tests, and, ultimately, by performance in the field. Thereafter, both by blood tests and by field experience, it will be possible to determine whether further inoculations beyond the course now recommended will be required—and if so, when. As for the resolution of the problem of vaccine safety, this is linked to an understanding of the dynamics of the virus inactivation reaction and the application of this knowledge. As for the resolution of the problem of effectiveness, this will come from an understanding of the dynamics of the immune process, upon the basis of which recommendations may be made; physicians and health officers can then apply vaccination to elicit its full potential effectiveness both in the individual patient and in the community as a whole.

The Mutation of Viruses.—In 1918 and 1919 influenza, known for centuries as a distressing but seldom fatal disease, suddenly turned virulent and swept across the world in the greatest epidemic of modern times. Then, just as suddenly, the fatal form of influenza disappeared, leaving some 25 million dead. Where had this scourge come from and where had it gone? At the time there was no accepted answer. We now know that influenza is a virus disease, and we believe that the 1918-1919 pandemic was simply a catastrophic example of biological mutation. . . . What chemical events occur when a virus mutates? . . . All known viruses have two chemical constituents: protein and nucleic acid. Like other proteins, virus proteins are very large molecules composed of much smaller units, the amino acids. The protein can easily be broken down into these units, and it is found that there are only some 20 different amino acids in even the most complex protein. Nucleic acids, found in all living cells, are also huge molecules. They can similarly be broken down into a few simple components; inorganic phosphate, two sugars and five organic bases. To the best of our present knowledge, these simple constituents of proteins and nucleic acids (with a few exceptional derivatives and close relatives) are the building blocks both of all viruses and of the chromosomes of all living things. . . . If the biological properties of a virus differ from those of its parent, is this difference reflected in the make-up of its protein? This question was investigated with the famous virus that causes the mosaic disease of the tobacco plant. . . . One of the most interesting results came out of the comparison of the original tobacco mosaic strain and a "killer" strain called J14D1. Young Turkish tobacco plants infected with the original strain suffer a characteristic mottling of the leaves accompanied by a certain amount of blistering, distortion and stunting. However, the plants continue to grow, reach maturity, flower and bear viable seed. Identical young plants infected with J14D1 are rapidly killed. Yet the killer strain differed from the original one only in its proportion of two amino acids: glutamic acid and lysine. Even in this proportion it differed from the original strain only by 10 to 20 per cent. In all other respects the two strains seem identical. This is a striking illustration of how small the chemical difference between a mild strain of virus and a killer may be.—C. A. Knight and D. Fraser, The Mutation of Viruses, *Scientific American*, July, 1955.

PUBLIC HEALTH IMPLICATIONS IN A PROGRAM OF VACCINATION AGAINST POLIOMYELITIS

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and
James A. Shannon, M.D., Bethesda, Md.

In public health and preventive medicine, the application of a new prophylactic agent, whether to large population groups or to an individual patient, requires careful consideration of many factors. The safety, potency, and efficacy of the agent are primary considerations. To these must be added problems of dosage, methods of administration, and the possibility of undesirable reactions in patients. In the case of large-scale immunization programs, account must also be taken of the cost and availability of the agent and the organization of personnel and facilities. These many technical, medical, and administrative problems must be weighed against the seriousness of the disease and the vulnerability of particular population groups. The use of the Salk vaccine against paralytic poliomyelitis has presented all of these general problems and some specific problems that were unanticipated by many individuals and groups working with the program. Our purpose is to present a brief report on some of these problems and the measures adopted for their solution.

PROBLEMS OF QUALITY CONTROL

The Biologics Control Law of the United States was first enacted in 1902. With minor changes, it was reenacted as Section 351 of the Public Health Service Act of 1944. Under this law, manufacturers are licensed by the Secretary of Health, Education, and Welfare, to produce specific biological products for interstate sale and for export. Licenses are issued by the Secretary upon recommendation by the Surgeon General of the Public Health Service. The minimum requirements to assure the safety, purity, and potency of each product are issued by the Public Health Service. The regulations governing biologics control are promulgated under the law by the surgeon generals of the Public Health Service, the Army, and the Navy, with the approval of the Secretary. Since 1902, the Public Health Service has maintained a biologics control unit staffed with competent scientists and devoted exclusively to the research, testing, inspectional, and administrative aspects of this statutory function. The legal responsibilities of the Public Health Service for promulgating standards for the quality control of biological products sold in interstate commerce have governed the official position that our organization has occupied in the 1955 poliomyelitis vaccination program.

Until April 12, 1955, however, poliomyelitis vaccine was an unlicensed, experimental product. The vaccine used in the field trials of 1954 was produced by commercial manufacturers under contract with the National Foundation for Infantile Paralysis, in accordance with specifications furnished by that organization. These specifications were drafted between December, 1953, and February, 1954, on the basis of information from numerous sources and were adopted by the National Foundation's vaccine advisory committee. Dr. Salk provided information about his own laboratory experience in the development and experimental testing of the prototype vaccine. The Connaught Medical Research Laboratories of the University of Toronto, Toronto, Canada, shared its experience in the growing of virus in large quantities by tissue culture methods. At the request of the Foundation, Dr. William Workman, Chief of the Laboratory of Biologics Control of the Public Health Service, and Dr. Joseph Smadel of the Army Medical Services Graduate School provided their expert knowledge of biologics manufacturing to aid in developing the specifications. The vaccine advisory committee expressed its confidence in the safety of the proposed product under the conditions prescribed in its specifications. Trivalent-pool material from each lot of vaccine used in 1954 was tested by the manufacturer, by Dr. Salk, and by the Laboratory of Biologics Control prior to final filling of the containers.

Production and testing in the first few months of preparation for the field trials were fraught with difficulties. Live virus was found in some preliminary lots that were rejected. The results of tests on specific lots varied in the three testing laboratories. However, by the time the vaccine advisory committee decided to go ahead with the field trial, two manufacturers had produced a series of lots consistently reported negative by all three laboratories. More stringent tissue culture tests had been incorporated in the requirements. Dr. Salk also had vaccinated 7,507 children with vaccine prepared by the manufacturers, with no harmful effects. This test was regarded as a good preliminary check on the safety of commercially produced vaccine. The Laboratory of Biologics Control had participated in all these developments. In recognition that manufacturers would apply for licenses to produce the vaccine, if the field trials were successful, the Laboratory, on May 20, 1954, issued tentative "Minimum Requirements, Poliomyelitis Vaccine." Vaccine manufactured prior to April 12, 1955, was prepared to meet these provisional standards.

Licensing and Production.—Immediately after the now-historic presentation of Dr. Francis' report on the 1954 field trial, a group of scientists met with the Chief of the Laboratory of Biologics Control at Ann Arbor, Mich., to advise on the licensing of production of the vaccine. The advisory group unanimously recommended licensing, and Dr. Workman transmitted his favorable

Surgeon General, U. S. Public Health Service, Department of Health, Education, and Welfare (Dr. Scheele), and Associate Director, National Institutes of Health, U. S. Public Health Service, Department of Health, Education, and Welfare (Dr. Shannon).

Read in the Panel Discussion on Prospects for the Control of Poliomyelitis before the Joint Meeting of the Section on Pediatrics and the Section on Preventive and Industrial Medicine and Public Health at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 7, 1955.

recommendation to the Surgeon General in Washington, D. C., who in turn recommended that the Secretary of Health, Education, and Welfare issue product licenses to the six firms whose applications were pending. These were the Cutter Laboratories; Eli Lilly & Company; Parke, Davis & Company; Pitman-Moore Company; Sharp & Dohme; and Wyeth Laboratories, Inc. The decision to license was based on the following factors. Each of the manufacturers is an established and reputable firm with which the Laboratory of Biologics Control has dealt for many years. Each held a general license to manufacture biological products. Each held licenses to produce numerous specific products. Each plant had been inspected during the period from September, 1954, through January, 1955, and the facilities for manufacturing and testing poliomyelitis vaccine had been found acceptable. The competence of the scientists in charge of production in each plant was known and respected. All but one firm (Sharp & Dohme) had had experience producing the vaccine in 1954. The manufacturers were considered to have overcome the earlier difficulties in obtaining a safe commercially produced vaccine. The Laboratory of Biologics Control had done complete tissue culture and monkey tests on six lots from five manufacturers (excluding Lilly) and numerous tissue culture tests on other lots from all manufacturers. The final factor in the decision to license was the evidence of safety and efficacy presented by Dr. Francis' evaluation of the field trials.

Thus, the national program of poliomyelitis vaccine release began on April 12. Stocks of vaccine were on hand, tested by the manufacturers in anticipation of licensing. Some lots had been completely tested at the National Institutes of Health, but tests on other lots had not been completed. Lots that had passed safety tests in the manufacturers' laboratories were released. No lot was released whose protocol did not show a clear record of performance in the manufacturer's tests. The situation with respect to poliomyelitis vaccine was unique. In contrast with the very slow, gradual development of other prophylactic agents, a great deal of experience in the use of this vaccine had been accumulated in the space of two years. The full record of events in the manufacture and testing of each lot (a protocol) had been successfully used for many years to evaluate the manufacturer's compliance with regulations or standards established for numerous biological products. The staff of the Laboratory of Biologics Control concluded that release on protocol review would be sufficient on this product.

In addition to Dr. Salk's trials with vaccine produced in his laboratory, covering approximately 14,000 individuals, more than 400,000 children had received commercially produced vaccine in 1954. The evidence from the field trial evaluation was interpreted to indicate the safety of commercial products, as prepared for that experiment. It was also believed that the manufacturers, armed with additional experience in production and with testing standards then thought to be adequate, would be able to prepare vaccine with a satisfactory margin of safety. The favorable experience with tests of numerous lots from all manufacturers was interpreted to support confidence in the process, the testing requirements, and the manufacturers' ability to apply them. During the last week of April, 1955, when cases of paralytic poliomyelitis were reported in children vaccinated with materials produced by the Cutter Laboratories, the Public Health Service immediately requested the withdrawal of all lots of that manufacturer's product that had been released previously. Simultaneously, a thorough investigation of the plant was instituted, and extensive laboratory tests of the material were begun. Studies of the production and testing of poliomyelitis vaccine in the hands of the other licensed manufacturers were also undertaken. The purpose of these studies was to review the total experience of the manufacturers in the production and testing of poliomyelitis vaccine, in order to determine whether there were common problems related to the basic method of production and the the adequacy of testing requirements. It was believed that should such common problems exist, steps could be taken to improve the methods of production and increase the adequacy of testing before additional lots of vaccine were released. The production records of all lots of vaccine that any firm had produced for the 1955 program, whether submitted for release or not, were studied. We then learned that such common problems had, in fact, existed. The producers had had difficulties in processing and testing some lots. If lots were clearly unsatisfactory, the manufacturers did not offer them for clearance, and therefore the protocols were not submitted and studied. The difficulties experienced by the manufacturers, as well as their successes, were now seen to provide valuable information that led the Public Health Service to require more adequate safety testing. The biologics control procedures in use prior to, and immediately after, April 12 had failed to provide adequate review of this total experience, with its inconsistencies in the behavior of a new and complex product, now being dealt with in large-scale production. In Cutter Laboratories' case, the health service is comparing that manufacturer's experience with the data recently accumulated from other producers, in an attempt to determine the extent to which the Cutter operation involved problems common with those of other manufacturers and the extent to which unique problems might account for the probable presence of active virus in a few lots of the Cutter material.

Decisions and Actions.—Outstanding virologists and epidemiologists from several private and public institutions have assisted in this review of manufacturing and testing procedures. Both technical and management representatives of all six licensed firms have cooperated fully in providing full information on their experiences. In brief, the information and advice derived from these studies and consultations during the past six weeks, have led to the following decisions and actions on the part of the Public Health Service: (1) request that the Cutter Laboratories withdraw all its supplies of poliomyelitis vaccine and initiation of thorough investigation, April 27; (2) activation of a Poliomyelitis Surveillance Unit in the Communicable Disease Center (PHS) to conduct epidemiological studies of poliomyelitis cases in vaccinated individuals, April 28; (3) initiation of additional laboratory studies of the vaccine from all manufacturers and halt in release of additional lots, April 30; (4) recommendation that the vaccination programs be halted until further information could be obtained on quality of

the vaccine, May 7 (based on presentation by manufacturer's technical representatives of new data on production problems); (5) inspections of plants of five licensed manufacturers, May 9-20, with subsequent clearance of some lots previously released and of additional lots awaiting release; (6) establishment (May 26) of a permanent Technical Committee on Poliomyelitis Vaccine to review lots of vaccine, to recommend action on them under the revised standards, and to guide future development of the vaccine program, seeking further improvements and refinements both in production and testing; and (7) revision of the minimum requirements for production and testing with announcement of the amended standards, May 26.

SCIENTIFIC BASES OF REVISED MINIMUM REQUIREMENTS

The body of new information acquired in the past six weeks is the basis of changes both in manufacturing procedures and testing. Although these changes have produced a dearth of vaccine at present, they will make possible a safer vaccine when the product begins to flow again in channels of distribution. Dr. Salk has presented in some detail the background of information upon which his contributions rest. What we shall present relates primarily to the problem of safety and originates in the demonstration that safety and effectiveness are not incompatible.

Strain Selection.—The selection of the Mahoney strain for the type 1 component of the vaccine requires special comment. This strain is characterized by great virulence because of its capacity to multiply rapidly in extraneural tissues. Because of this characteristic, it is at least theoretically possible for a minute dose of living virus to produce incapacitating paralysis. The hazard of the Mahoney strain has led some virologists to criticize its inclusion in the Salk vaccine, despite its ability to induce a high titer of type 1 antibody. This objection has led those responsible for vaccine development in Denmark to exclude it in their routine vaccine production this spring. They have used the Brunhilde strain and have compensated in part for its poorer antigenic properties by including proportionately more type 1 antigen than types 2 and 3 in the final vaccine.

Inactivation.—An important feature of Dr. Salk's conception of the preparation of a suitable vaccine lies in the principle that presumes a large margin of safety in the inactivation process itself.[1] This point warrants discussion. Figure 1 shows the theoretical course of an inactivation process as envisaged by Dr. Salk. It starts with the concentration of tissue culture infective doses of one million per milliliter, a common concentration. During the initial phase of the inactivation process, the log of the virus concentration falls linearly with time, and 48 to 72 hours later reaches zero. At this time, the concentration of live virus is 1.0 tissue culture infective unit per milliliter of viral suspension. Figure 1 has been drawn to show the intercept time of the inactivation curve and zero at three days. By extrapolation, the concentration is assumed to be reduced to 1.0 tissue culture infective unit per one million milliliters at six days, and 1.0 tissue culture infective unit per 1.0×10^{-12} ml. at nine days. This concentration is of such a low order that its significance can be grasped only when the numbers are reduced to common terms. The prediction means that if the reaction proceeds as indicated in figure 1, there will be a concentration of living virus in the order of 1 tissue culture infective unit in each million tons of inactive viral suspension, at the end of nine days. During the production of field trial vaccine, when the initial part of the reaction was shown to proceed according to the original concept, the single strain pool was considered suitable for pooling without further examination for live virus.

There are alternatives to this theoretical conception. The viral suspension is not a monophasic system but consists of a number of discrete particles in suspension. At high concentrations, these may behave in a manner not dissimilar to a monophasic system, and during the first period of inactivation process the system may yield data that are describable by a simple equation derived from the law of mass action. However, with the progression of the reaction and at lower live particle concentrations, the heterogeneity of the system should assert itself. The course of the reaction under this circumstance may depart from that of a simple first-order reaction, as derived from the law of mass action or from concepts of surface chemistry of a simple system. In high dilution, the residual live virus will probably consist of particulates of varying size and shape and in varying degrees of aggregation. Particulates contained in such a mixture cannot be expected to inactivate at the rate calculated from the behavior of the reaction during its initial phase. During this phase, the reaction will be dominated by that portion of the particulate mass that is more easily inactivated. This would appear to be the bulk of the material undergoing inactivation. The extent to which the inactivation process departs from a straight line, even in the initial phase, will be a reflection of the extent to which the particulate mass is composed of particulates

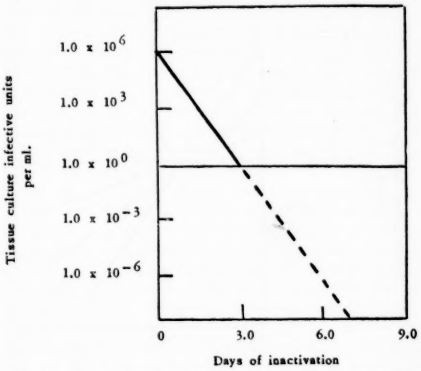

Fig. 1.—Theoretical curve of inactivation of poliomyelitis virus (after Salk).

1. Salk, J. E., and others: Formaldehyde Treatment and Safety Testing of Experimental Poliomyelitis Vaccines, Am. J. Pub. Health 44:563-570 (May) 1954.

of differing sensitivity (an index of heterogeneity) and the extent to which there are other physical and chemical variations in different proportions of the total suspension (problems of mixing).

These considerations have a practical bearing on manufacturing problems. Heterogeneity in the system can operate to remove the so-called built-in factor of safety. This consequence is demonstrated graphically in figure 2. The system is obviously more complex than is given in this example, which merely points up the importance of a minute portion of the initial virus mass in conditioning the later stages of the reaction. Additional formal treatment is not warranted. In figure 2, curve *A* describes the reaction proceeding in the original conception (fig. 1) when the concentration of live virus at the beginning of the reaction is one million per milliliter (1.0×10^6). Curve *B*, in which the initial live virus concentration is taken to be 1,000 particles per milliliter, shows a similar reaction proceeding at a rate one-half as fast as in curve *A*. In curve *C*, the rate is one-fourth of

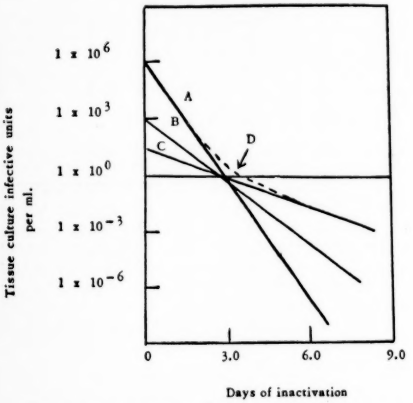

Fig. 2.—Inactivation of poliomyelitis virus. *A*, reaction when concentration of live virus at the beginning is one million per milliliter. *B*, initial live virus concentration is 1,000 per milliliter. *C*, initial live virus concentration is 32 per milliliter. *D*, composite inactivation curve of a mixture of the three.

A and the initial live virus concentration is taken at 13 particles per milliliter. The composite inactivation curve of a mixture of the three is shown as curve *D*. Starting with a suspension composed of the three types of particles in the assumed concentrations, the summation of the three reactions will be dominated by reaction rate of curve *A* initially and of curve *C* at a later time. Hence, we may conclude that observations during the initial phase of the reaction do not constitute an adequate basis for judgment of the course of the remainder of the reaction in these circumstances.

Another factor argues against acceptance of the original concept as a basis for an interrelated combination of inactivation and safety. The suspending solution contains protein coagulable by formaldehyde, which favors the formation of viral particulates occluded in minute protein precipitates not generally distinguishable to the eye. Such particulates would be relatively inaccessible to the inactivating formaldehyde. The extent to which a combination of the foregoing factors influences the course of inactivation will also be reflected in the extent to which the actual curve of inactivation departs from a straight line.

SAFETY TESTING

A safety test, generally speaking, is a laboratory procedure utilized as a part of quality control to separate that which is unsuitable from that which is suitable. Safety tests for the Salk poliomyelitis vaccine were devised mainly to find contamination and process failures from accidents in manufacture and not to detect small amounts of residual live virus that the process was believed to have reduced to an immeasurably low, harmless level. The primary safety data were conceived as being those that described the initial stages of the inactivation process. The prime factor of safety, according to the original conception, was built into the process of inactivation. However, insofar as the process departs from that theoretical conception, whether because of deficiency in the conception or because of inadequacies in the handling of the process, the safety testing becomes of increasing importance both as a guide to processing and as a final determinant for safety. The two tests for the presence or absence of live virus utilized in the quality control of the vaccine are the monkey test and the tissue culture test, in routine manufacture.

Monkey Test.—The monkey test is very crude, as was demonstrated in the spring of 1954, incidental to the preparation of material for the field trial. This will not be discussed, except to point out that the inability of this test to discriminate between vaccines containing low concentrations of live virus demonstrable by tissue culture and those containing none, has been the common experience of each of the manufacturers. Their data show repeatedly that live virus detectable by tissue culture is not detected by the monkey test as presently performed. Consideration should be given to increasing the sensitivity of the monkey test by concentration of the test material. Otherwise the test should be discarded.

Tissue Culture Safety Test.—Certain assumptions have been made as a basis for analysis of the sensitivity and reliability of the tissue culture safety tests. In general, these assumptions provide an estimate of greater reliability than actually obtains. A somewhat comparable analysis with respect to vaccine for foot-and-mouth disease has been made by Henderson,[2] and include the following assumptions. 1. Residual live virus can be defined in terms of the number of discrete particulates, varying from zero to some finite number, contained in a unit volume (1.0 liter) of antigen suspension. 2. Random distribution (truly effective mixing) of these particulates obtains. 3. One particulate is an effective dose for a sensitive tissue culture preparation. More than one particulate is required for an insensitive tissue culture preparation or for an infection in a series of relatively nonsensitive tissue culture preparations. 4. The total volume of virus suspension is no less than 10 liters.

2. Henderson, W. M.: Significance of Tests for Non-Infectivity of Foot-and-Mouth Disease Vaccines, J. Hyg. **50**:195-208 (June) 1952.

Certain statistical probabilities have been calculated, using the Poisson distribution, which is applicable in this case. Table 1 shows the probability of failing to demonstrate live virus at different concentrations when different size samples are tested. Table 2 shows the chances of picking up a positive lot, when the upper level of acceptable viral concentration is set at 5 infective units per liter and with the sample volumes commonly used by each of the manufacturers of the vaccine. One milliliter was tested in tissue culture for each liter of single-strain and polyvalent pool. It is quite apparent that different standards of acceptability as regards the possible presence of infective particles have been incorporated into the processes of the different manufacturers. This variation stems from the erroneous assumption inherent in the "Minimum Requirements of April 12, 1955" that the volumes used in the tests should be directly proportional to the total volume tested. Routine testing on such assumptions would not provide a reasonable assurance of the absence of live virus in the finished vaccine of certain of the manufacturers. It is important to note, however, that the volume of material tested in clearing vaccine for the field trial in 1954 would place an even lower value of confidence in this material. A more rational basis for safety testing has been adopted. The objective has been to design a testing procedure that will identify lots of vaccine containing more than a given concentration of live virus particulates. Such a procedure does not bear upon the level of viral concentration that will be infective to man. (Actually the determination of the infective level for man is today beyond the possibility of direct examination.)

TABLE 1.—*Size of Sample Needed to Keep Probability of Getting Negative Test Result Below Specified Level at Certain Postulated Concentrations of Particulates Containing Live Virus and at Two Levels of Test Sensitivity in Lots of Ten Liters or More*

Probability of Getting Negative Result	Assumed Concentration of Infectious Unit per Liter: 5	10	100
Test Sensitivity Level 1			
One Particulate Required for Positive Test. Sample Required, Ml.			
0.10	460	230	23
0.05	600	300	30
0.01	920	460	46
0.001	1,380	690	69
Test Sensitivity Level 2			
Two Particulate Required for Positive Test. Sample Required, Ml.			
0.10	778	389	39
0.05	948	474	47
0.01	1,328	664	66
0.001	1,846	923	92

MANUFACTURING EXPERIENCE

The systematic survey conducted in each of the plants producing poliomyelitis vaccine has been mentioned. Some of the results of this survey are presented here. The process of inactivation of the poliomyelitis vaccine when done on a large scale does not seem to follow the original concept in the hands of any manufacturer with any degree of reliability, as shown in part by a curvilinear, rather than a straight-line, relation between time and the log of the residual live virus in the initial phases of the reaction. It is also evidenced by the frequent occurrence of a positive tissue culture test from 9 to 12 days after the beginning of the inactivation process. It is also apparent that the inactivation process has not yielded consistent results in the hands of most of these manufacturers. That is to say, the initial test performed at the time when all live virus was presumed to have been inactivated shows that an appreciable proportion of single-strain pools still contained live virus (table 3). This is an important finding. It demonstrates that the departure of the process from the theoretical conception greatly diminishes the factor of safety that was believed to have been built into the basic process. Consequently, principal reliance for the exclusion of live virus must be placed upon the safety test in the final vaccine.

TABLE 2.—*Size of Sample Used in Safety Testing, by Tissue Culture, Prior to May 22, 1955*

Laboratory	Size of Sample, Ml.: Single Strain Pool	Polyvalent Pool	Chances of Picking Up Positive Lot,* %
A	60	150-175	70
B	500	360	99
C	400-500	1,200-1,600	Over 99.9
D	25	300	80
E	40-45	140	60-70

* Assuming lot had five tissue culture infectious doses per liter and assuming high sensitivity for all tissue cultures.

The data on the safety tests performed immediately after combination into trivalent pools offer further evidence of inadequacy (table 4). Live virus was frequently found in a trivalent pool when this had been presumed to be free of live virus on the basis of testing applied to the monovalent pools that composed it. In the hands of certain manufacturers (for example, laboratory C), when the trivalent pools were formed prior to the completion of the safety tests of the single-strain pools, it was impossible to predict the outcome of the tests (table 5). One can only conclude from such data that the tissue culture test for active virus, as applied to the single-strain pool, was not an adequate process guide, nor did it provide a sense of security that sizeable concentrations of live virus would not be included in the trivalent pool. This again emphasized the inadequacy of the safety tests as performed during the period of processing and placed an even greater burden on the final safety testing of the trivalent pool just prior to subdivision and packaging.

TABLE 3.—*Positive Single Strain Pools on Initial Test*

Laboratory	Lots: No.	% Positive
All	869	11
A	97	21
B	234	19
C	85	8
D	267	5
E	126	2

Detailed tables show an almost random distribution of positives in relation to processing data. Positive tests occurred in a sufficiently high proportion of instances to minimize the reliability of a single subsequent negative

test, whether used for process control or as a final test of safety (table 6). These data summarize the experience of laboratory B in reprocessing single-strain pools after a positive tissue culture test. Of a total of 234 single-strain lots tested, 44 were positive on the original test. These were reheated at 37 C for an additional two to three days, after which negative tests were obtained from 21 lots. Some of the remaining lots

TABLE 4.—*Positive Trivalent Pools on Initial Tests*

Laboratory	Lots	
	No.	% Positive
All	127	13
A	21	33
B	34	9
C	22	23
D	8	..
E	42	4

were then subjected to a second inactivation period, resulting in negative tests for nine. Two continued to show positive tests; a third continued to be positive after three inactivation periods. The remaining 11 pools were otherwise disposed of and do not bear on the problem of inactivation.

That repeat testing favors the occurrence of negative tests by chance, even if reinactivation is ineffective, is indicated by the data in table 7. Here, 32 polyvalent pools are examined in relation to their history. Twenty-three were negative in the initial test of their single-strain pools, as well as in the trivalent pools. The remaining nine polyvalent pools contained at least one positive single-strain pool that had been combined into a trivalent pool after reinactivation. Three of these nine showed a positive tissue culture safety test in the trivalent pool.

In summary, the plant data show departures from the theoretical data, as well as a lack of discrimination in the previous safety testing practices. There are exceptions to certain of these criticisms, but these need not be

TABLE 5.—*Relation of Tissue Culture Results in Single Strain Pools and Polyvalent Pools When Tests Are Done Independently* *—*Laboratory C*

		Polyvalent Pools		
		Negative	Positive	Total
Single Strain Pools	Negative	12	3	15
	Positive	5	2	7
	Total	17	5	22

* Single strain pools were combined into polyvalent pools before results of tissue culture tests on individual pools were known. The tests are, therefore, independent, offering an experiment of opportunity on the chance nature of results apparently obtained. Of 10 lots with positive results obtained by tissue culture in either single strain pools or in the polyvalent pools, only 2 showed positive results both before and after pooling.

discussed here, since the examination of the data has been aimed primarily at finding weaknesses in the process, some of which were found in each laboratory.

FORMULATION OF NEW STANDARDS

As a result of the foregoing considerations, it has been possible to develop definitive modifications of the safety requirements controlling the manufacture of poliomyelitis vaccine. 1. Single-strain pools are to be inactivated in 1:4,000 formaldehyde at 37 C, for such a period of time as will permit the obtaining of two consecutive negative tissue culture tests separated by a three-day interval prior to the termination of inactivation. In order to assure the exclusion of live virus particulates above a minimal concentration, the volume of single-strain pool material used for each safety test must not be less than 500 ml. In application, this means a negative tissue culture test on the sixth to ninth day from the beginning of inactivation and a second negative tissue culture test three days thereafter. Observations during the early part of the inactivation process can be limited to the demonstration that the process is proceeding as usual, and no dependence need be placed on the precise rate of initial fall in the concentration of live virus. 2. Once having obtained a positive tissue culture test after the initial inactivation period, only one additional inactivation period is permitted. During this retreatment, two negative tissue culture tests must be obtained on a volume of not less than 500 ml. each, separated by three days. 3. The trivalent pool is to be considered suitable for vaccine manufacture if a negative tissue culture test is obtained, utilizing 1,500 ml. of the pool in the tissue culture test.

TABLE 6.—*Reinactivation History of a Number of Single Strain Pools—Laboratory B*

Single Strain Lots Tested	No.
Total	234
Negative on original test	190
Positive on original test	44
Reinactivated once with negative test	21
Reinactivated, positive test; second reinactivation with negative test	9
Reinactivated, positive test; second reinactivation with positive test; rejected	2
Three reinactivations, each followed by positive test	1
Reinactivation started, but test incomplete	7
Accepted on repeat testing of same sample without reactivation	4

4. Industrial practices relative to stirring for purposes of processing and sampling, as well as to temperature and pH control, must be such as to produce consistent inactivation. 5. Finally, breaks in manufacturing routine are excluded through a test for live virus in final container material.

The application of the above recommendations to the production of poliomyelitis vaccine should result in a product essentially free of live virus. With negative results at the recommended test volumes in two consecutive tests during initial inactivation, or following a single reinactivation period for each single-strain pool, and with a third negative on the trivalent pool, final vaccine should contain 5 or more tissue culture infective units per liter less than once in 100,000 times. Additional operational refinements can also be added in the routine production of the vaccine, which should result in further improvements in product, lessening of costs, and no loss of safety. These suggestions, which have been discussed with the manufacturers at length, include: the substitution of less virulent type 1 strains for the Mahoney strain, control tests to document the sensitivity of the tissue culture for virus particulates, concentration of the viral suspension before applying the safety tests, the conduct of the safety tests themselves, and modification of physical arrangements during processing.

EPIDEMIOLOGICAL EXPERIENCE, APRIL TO JUNE, 1955

When, on April 25, the first report was received of a case suspected to be poliomyelitis in a vaccinated child, a medical officer from the Communicable Disease Center of the Public Health Service was dispatched to participate in an epidemiological study of the case. During the 1954 field trial, personnel of the Center's Epidemic Intelligence Service had participated in the study of illnesses occurring in both vaccinated and control groups, under the direction of Dr. Francis. In anticipation of the need for epidemiological studies of poliomyelitis in the 1955 program, the Public Health Service, prior to April 12, had planned a small surveillance program to assist state health departments in the follow-up of cases. On April 28, this program was established as a Poliomyelitis Surveillance Unit on an expanded scale, with instructions to devote full time to the rapid identification of cases of paralytic poliomyelitis in vaccinated children and to conduct thorough epidemiological studies of each case. This nationwide epidemiological investigation of poliomyelitis cases associated with vaccination will continue in operation throughout 1955. It is made possible by the collaboration of state and local health officials, private physicians, and the directors of numerous public and private laboratories, with the field and headquarters

TABLE 7.—*Relation of Tissue Culture Test Results in Single Strain and Polyvalent Pools—Laboratory B*

		Polyvalent Pools		
		Negative	Positive	Total
Single Strain Pools	Negative	23	..	23
	Positive, then after re-inactivation, negative.	6	3	9
	Total	29	3	32

staff of the Public Health Service. The data that follow are derived from the daily reports of the Poliomyelitis Surveillance Unit through May 31, 1955. This information has been an important factor in guiding our decisions and actions with respect to the vaccination program. Since many cases are still under investigation, some of these figures are subject to confirmation or change.

Poliomyelitis Associated with Vaccination.—Table 8 shows the numbers of paralytic and nonparalytic cases of poliomyelitis associated with the product of each manufacturer whose materials have been used since April 12. Attack rates, based on the approximate number of recipients of each product, are shown. A total of 114 cases, with five deaths, had been reported from April 25 through May 31, occurring among approximately 5,500,000 persons within one month after injection of poliomyelitis vaccine. Of these cases, 78 were paralytic and 36 nonparalytic. The largest number of cases and the highest attack rate occurred among approximately 409,000 recipients of vaccine produced by the Cutter Laboratories. Sixty-one per cent of all cases and 76% of the paralytic cases have occurred in Cutter vaccines, with an attack rate of 17 per 100,000 in one month, as contrasted with rates of 1 per 100,000 or less in the four remaining groups. Forty-nine of the Cutter-associated cases occurred in California and Idaho. The remaining 20 cases associated with this product have developed in 15 other states throughout the country.

Among approximately 5 million persons who have received the products of four other manufacturers, 45 cases had been reported as of May 31. Twenty of these were paralytic. The 10 paralytic and 20 nonparalytic cases associated with the Eli Lilly product have occurred chiefly in southeastern and southwestern states where

TABLE 8.—*Cases and Attack Rates in Individuals Receiving Poliomyelitis Vaccine, with Onset April 20-May 21, 1955*

Vaccine Manufacturer	Approximate No. of Persons Receiving Vaccine	Cases			Total Attack Rates per 100,000 per Month
		Paralytic	Non-paralytic	Total	
Cutter	409,000	59	10	69	17
Lilly	2,514,000	10	20	30	1
Wyeth	776,000	7	4	11	1
Parke-Davis	1,234,000	2	0	2	1
Pitman-Moore	461,000	0	2	2	1
Totals	5,394,000	78	36	114	2

poliomyelitis was occurring spontaneously. The 11 Wyeth-associated cases have been reported from midwestern and eastern states. The two cases associated with Parke-Davis material were reported in Illinois, and the two Pitman-Moore-associated cases were reported in Nebraska. It must be emphasized that association does not necessarily mean a cause-and-effect relationship.

Numbers of Cases Reported and Numbers Expected.—There is general agreement that cases of poliomyelitis may be expected to occur, by coincidence, following vaccination because the vaccine will not be absolutely effective and because it will be given to some children who harbor the virus and do not have apparent poliomyelitis at the time of vaccination. Table 9 presents an attempt to determine whether cases among children vaccinated in the 1955 program have been more common than would have been expected by chance. The ages of the first-grade and second-grade children who received vaccine in the National Foundation clinics are known with suffi-

TABLE 9.—*Reported Versus Expected Cases in Children Receiving Poliomyelitis Vaccine in National Foundation Clinics*

Vaccine Manufacturer	Approximate No. of Persons Receiving Vaccine (Foundation Clinics)	No. of Poliomyelitis Cases, from April 20-May 21	
		Reported	Expected
Cutter	309,000	35	5
Lilly	2,514,000	28	24
Wyeth	776,000	11	2
Parke-Davis	834,000	2	3
Pitman-Moore	411,000	2	2

cient accuracy to calculate the numbers of expected cases. Data supplied by the Foundation also make it possible to determine the geographical areas in which these children were vaccinated, as well as the sources of the materials injected. It is not possible, however, to compare the poliomyelitis experience of these children with the current experience of unvaccinated 6, 7, and 8-year-olds in the same geographical areas. A very high proportion of children in these age-groups have received vaccine, leaving virtually no "control" group for com-

parison. Expected numbers, therefore, have been calculated by applying the five-year (1950-1954) median attack rate in 6, 7, and 8-year-olds in the specified geographical areas to the numbers of first-grade and second-grade children vaccinated in 1955 in the corresponding areas. This is a crude measure, for the incidence of poliomyelitis varies widely and unpredictably in successive years; but it is the best tool available under present conditions. The sevenfold increase of poliomyelitis cases over expected incidence in children vaccinated with Cutter materials is statistically significant. However, the marked year-to-year variations observed in attack ratio in any given locality and the small number of cases related to the Wyeth product preclude an accurate interpretation of the data. The numbers related to the Wyeth product are too small to permit accurate interpretation. The numbers of cases reported among children who received vaccines made by Eli Lilly, Parke-Davis, and Pitman-Moore were within the range expected by chance occurrence.

Evidence Related to the Presence of Infective Virus.—The data accumulated by the Poliomyelitis Surveillance Unit support the hypothesis that the excess cases among individuals vaccinated with Cutter material resulted from the use of some lots of vaccine containing infective virus. No other cases of poliomyelitis had been reported in Idaho and in some of the California areas, and this created a suspicion that there might be active virus in some of the vaccine. This suspicion has been buttressed by data on the time intervals between inoculation and onset of paralysis; by a close correlation between the site of inoculation and the site of first paralysis; by the occurrence of poliomyelitis in household associates of vaccinated children; and by the isolation of poliomyelitis virus by one laboratory, from a lot produced by Cutter. Table 10 shows the time intervals between inoculation and onset of paralysis in 66 paralytic postvaccination cases, by source of vaccine. It shows also the comparable interval in 32 monkeys experimentally infected with poliomyelitis virus by Dr. David Bodian.[3] The time intervals in Cutter-associated cases ranged from 5 to 20 days, with a median of 9 days. In three-fourths of the cases, first paralysis occurred from 6 to 14 days following vaccination. This finding corresponds with the comparable incubation periods in monkeys infected by intramuscular injection of virus. Moreover, chronological distribution of cases after inoculation of Cutter materials is the same distribution expected in a common-source outbreak after one exposure to the infectious agent.

TABLE 10.—*Poliomyelitis Cases, by Interval Between Inoculation of Poliomyelitis Vaccine and Onset of Paralysis*

Interval, Days	No. of Cases of Poliomyelitis in Persons Inoculated with Vaccine Produced by:				Experimental Data in Monkeys *
	Cutter	Lilly	Wyeth	Parke-Davis	
5-7	8	2	0	0	3
8-10	22	4	1	0	12
11-13	8	0	1	0	9
14-16	9	1	0	1	3
17-19	2	1	1	0	3
20-25	1	1	3	0	2

* Bodian.[3]

3. Bodian, D.: Viremia in Experimental Poliomyelitis: II. Viremia and the Mechanism of the "Provoking" Effect of Injections or Trauma, Am. J. Hyg. **60**:358-370 (Nov.) 1954.

Table 11 compares the sites of inoculation and first paralysis in postvaccination cases, by source of vaccine, with the corresponding sites in monkeys inoculated with live virus. The Cutter-associated cases show a high degree of correlation between the site of inoculation and the site of first paralysis. In 43 of 55 such cases, or 78%, the first paralysis occurred in the same arm or leg that was injected with the vaccine. This finding is strikingly similar to the experimental evidence in monkeys. In contrast, only 1 of 10 Lilly-associated cases shows the same relationship. There are too few paralytic cases associated with Wyeth and Parke-Davis materials to warrant conclusions. A number of poliomyelitis cases have developed among parents and siblings of vaccinated children. As of May 31, 50 such cases had been reported, 36 of which were in the families of children vaccinated with Cutter materials. Eli Lilly and Wyeth materials were associated with five and nine family contact cases respectively. Forty-one of these cases were reported as paralytic, with three deaths. They are distributed among sources of vaccine as follows: Cutter, 29; Lilly, 5; and Wyeth, 7. About half of the cases have occurred in parents and half in siblings. No vaccinated children in these families had contracted paralytic poliomyelitis, but about one-third of them had a minor illness within two weeks after inoculation and prior to the onset of poliomyelitis in other members of the family.

TABLE 11.—*Poliomyelitis Cases in Persons Receiving Vaccine, by Site of Inoculation and Site of First Paralysis*

Sites of Inoculation and First Paralysis	Poliomyelitis in Persons Inoculated with Vaccine Produced by:								Experimental Data in Monkeys *	
	Cutter		Lilly		Wyeth, No.	Parke-Davis, No.				
	No.	%	No.	%					No.	%
Same	43	78	1	10	3	1			23	72
Different	12	22	9	90	4	1			9	28
Totals	55		10		7	2			32	

* Bodian, D.: Unpublished data.

Isolation of Virus.—Type 1 poliomyelitis virus has been isolated from more than 20 cases in children vaccinated with Cutter materials and from 2 associated with the Wyeth product. Type 2 virus has been isolated from one case and type 3 from another, both associated with Lilly materials. Laboratory work on postvaccination cases is in progress, and other isolations no doubt will be reported. Dr. Louis P. Gebhardt, department of bacteriology, University of Utah College of Medicine, in an independent study, has reported the isolation of type 1 poliomyelitis virus from a vial of vaccine produced by the Cutter laboratory and issued in one of the lots associated with paralytic cases in children vaccinated with this material. Extensive studies of all lots issued by this manufacturer are in progress at the National Institutes of Health and other outside reference laboratories and have not yet been completed. The Public Health Service final report on the Cutter plant and vaccine will be made when vaccine tests are completed.

"Provocation" Phenomenon.—In our investigation of postvaccination cases, we have considered the hypothesis that involvement of the central nervous system may be precipitated by intramuscular injection of vaccine in in-

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dividuals already infected with poliomyelitis virus. Had this hypothesis been applicable, one would have expected the excess paralytic cases to occur in areas known to be experiencing some poliomyelitis, such as the southern states. The excess cases did not adhere to this pattern; instead they occurred unexpectedly in Idaho, where no cases other than those associated with the Cutter product were observed. Excess cases did not occur in the southern states up to May 31, where a very large number of children were vaccinated with the product of Eli Lilly, at a time when poliomyelitis was known to be present. Thus, available data do not support the "provocation" hypothesis as an explanation of excess of paralytic cases in areas where Cutter materials were used.

EPIDEMIOLOGICAL CONSIDERATIONS FOR THE FUTURE

The current shortage of poliomyelitis vaccine will undoubtedly continue for some months to come. There is no question, however, that increasing amounts will be prepared; all of the licensed firms have indicated their desire to continue production under the amended requirements. During the period of short supply, physicians can be expected to limit the use of the vaccine to children in the most susceptible age groups, and parents must be satisfied to have it so used. The decision of whether to vaccinate an individual, or to vaccinate during the period of peak incidence, or to vaccinate during local epidemics of the disease rests with the physician and health officer. State and local health officials also should give advice, based on their knowledge of the local, state, and nation-wide prevalence of poliomyelitis. The role of the Public Health Service is related to standards of purity, potency, and safety of the vaccine, to epidemiological studies of the disease, and to the issuance of recommendations on vaccination problems when appropriate. There can be no doubt that the use of the vaccine this season will prevent a high percentage of paralytic poliomyelitis cases in vaccinated children in the age groups identical with those studied in the field trial. For every vaccinated child who contracted paralytic poliomyelitis in the placebo-control areas during the 1954 field trials, three to four children in the placebo groups experienced paralysis.[4]

It must be emphasized, however, that the only substantial data on the effectiveness of the vaccine in preventing paralytic poliomyelitis are limited to children 6 to 9 years of age. Dr. Salk has presented data showing that children under age 6 developed antibodies after vaccination. The relationship between antibody development and protection against paralytic poliomyelitis is still under study. The field trial provided no data upon which to estimate the degrees of protection following vaccination of children under 6 and over 9. Although the data show substantial protection among vaccinated children in the placebo areas, they also show that the degree of protection afforded the children decreased progressively with their age. The downward trend from 9 to 6 years was striking, and the 6-year-olds received little protection. The latter observation, however, may be related to observation of too small a group.

When it becomes possible to use the vaccine in children of age groups other than 5 to 9, it is hoped that careful epidemiological studies will be made to determine the effectiveness of the vaccine in children at younger and older age levels than those who were studied in 1954. Experience with other prophylactic agents indicates that satisfactory procedures for the control of a disease evolve progressively. For example, no substantial control of diphtheria was possible until a satisfactory prophylactic for use in infants and young children had been perfected and effective methods for its application had been developed. This development occurred over a period of many years. This is not to suggest that we shall be so long in perfecting our procedures for the control of poliomyelitis. There are, however, many gaps in our knowledge of poliomyelitis vaccine application. Optimum dosage, time interval between injections, the duration of immunity after vaccination, and the possibility of combining the vaccine with other prophylactic agents and adjuvants are a few of the problems that must stay under constant study with respect to this vaccine. Current research in Dr. Salk's laboratory and many other institutions may make important contributions to the control of poliomyelitis in the next few years. Studies in virology and immunology, not directly related to the vaccine, will have an important bearing on control of the disease. Much is being learned about the mutations of viruses. Moreover, work is in progress on poliomyelitis vaccine produced by a different method of inactivation, as well as on attenuated virus vaccines. Although it is too early to evaluate these new developments in terms of clinical use, they serve to remind us of the essentially dynamic nature of medical science. The development and use of the Salk vaccine has opened the door on a new period in the control of poliomyelitis. Continuing research and observation will surely lead to further improvements and to eventual control of the disease. American medicine and public health have been capable of taking advantage of new medical discoveries in the past. There is no reason now to doubt that they will not take full advantage of the new opportunities afforded preventive medicine by the development of a poliomyelitis vaccine by Dr. Jonas Salk.

SUMMARY

It is erroneous to assume that absolute safety can be assured, but it is believed that recently amended requirements for manufacture and safety testing of poliomyelitis vaccine assure the production of potent material that is safe, as tested by present tests for active virus detection, and that the risk of such vaccine transmitting poliomyelitis is negligible. Vaccine produced by four licensed manufacturers has been used in approximately 5 million children in 1955 with no untoward results. A total of 114 cases of poliomyelitis have been reported in vaccinated individuals through May 31. Of these, 79 were associated with the product of one manufacturer, which had been used in a total of approximately 409,000 per-

4. Francis, T., Jr., and others: Evaluation of 1954 Field Trial of Poliomyelitis Vaccine: Summary Report, Am. J. Pub. Health **45**:1-63 (May, pt. 2) 1955.

sons. The widespread use of the poliomyelitis vaccine can be expected to prevent a high percentage of paralytic poliomyelitis cases, especially in children 6 to 9 years of age, and probably in other age groups as well, when supplies become available. It is believed that children younger than 6 years, children older than 9, and adults should receive the vaccine and that studies should be made to ascertain its preventive value against paralytic poliomyelitis in these age groups. Additional experience with the vaccine in the hands of private practitioners and public health officers will lead to further improvements in the control of poliomyelitis. Final decisions on the use of the vaccine remain the responsibilities of individual physicians and health officers.

1954 POLIOMYELITIS VACCINE FIELD TRIAL

PLAN, FIELD OPERATIONS, AND FOLLOW-UP OBSERVATIONS

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Early in 1953 Salk reported that a formaldehyde (Formalin)-treated virus vaccine, prepared in his laboratory, had produced neutralizing antibodies against all three types of poliomyelitis virus in children who possessed no demonstrable circulating antibodies against these viruses before vaccination.[1] This trivalent vaccine appeared to be noninfectious; inoculation of human subjects was free of untoward reactions. Moreover, the method of inactivation with formaldehyde, developed at the University of Pittsburgh Virus Research Laboratories, appeared to provide a wide margin of safety in dissociating virus infectivity from its antigenic properties. Inactivation proceeded as a first order chemical reaction, thus permitting ready standardization and rigid control. Experiments in progress gave promise of the early development of even better antigens, capable of inducing persistently high levels of neutralizing antibodies comparable to those observed in individuals who had experienced naturally occurring infection and clinically recognized disease.

Immediately after publication of this report, a distinguished group, aware of the social as well as the scientific implications of these observations, concluded that only a meticulous and systematic extension of Dr. Salk's work could adequately determine the effectiveness of the experimental vaccine under conditions of epidemic exposure. The recommendations of this group, supported by editorial comment in THE JOURNAL,[2] were set forth in an open letter to the medical profession, signed by Dr. Thomas M. Rivers, director of the Hospital of the Rockefeller Institute for Medical Research.[3] The step-by-step plan and time table outlined in this letter provided the guide lines to which the National Foundation for Infantile Paralysis has rigidly adhered in the field trial of the vaccine. In advance of the 1953 season Salk had administered the vaccine to approximately 600 individuals, of whom 474 were children between the ages of 4 and 12. None contracted clinical poliomyelitis during the season of observation; seven were known to have been exposed to the disease through intimate contact, and three of these seven may be presumed to have been infected as a subsequent rise in circulating antibody titers was detectable.[4] Salk's observations followed closely upon other notable advances in the understanding of the pathogenesis and immunology of poliomyelitis. In 1949, Bodian, Morgan, and Howe established the existence of at least three distinct types of poliomyelitis virus.[5] Soon thereafter cooperative research in four different university laboratories confirmed these findings. This typing program, sponsored by the National Foundation, suggested that efforts to control poliomyelitis by immunologic means need be concerned only with the three varieties of the virus that had been isolated from human infections.[6]

Concurrently in 1949, Enders and his associates demonstrated that the poliomyelitis virus could be propagated in non-nervous tissue.[7] This not only supported the hypothesis that the virus might multiply elsewhere in the body before reaching the central nervous system but also offered a practical means of growing the virus in tissue culture. This provided a suitable technique for the mass production of virus necessary for large-scale manufacture of the vaccine. Then, in 1952, Horstmann [8] and Bodian [9] independently found poliomyelitis virus circulating for a brief period in the blood during the prodromal stage of disease, thus indicating a possible site for the establishment of an immunologic barrier to the paralytic sequel of infection. In the following year,

Medical Consultant, Vaccine Division, National Foundation for Infantile Paralysis.

Read in the Panel Discussion on Prospects for the Control of Poliomyelitis before the Joint Meeting of the Section on Pediatrics and the Section on Preventive and Industrial Medicine and Public Health at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 7, 1955.

1. Salk, J. E., and others: Studies in Human Subjects on Active Immunization Against Poliomyelitis: 1. A Preliminary Report of Experiments in Progress, J. A. M. A. **151**: 1081-1098 (March 28) 1953.

2. Research on a Vaccine for the Prevention of Poliomyelitis, editorial, J. A. M. A. **151**: 1198 (April 4) 1953.

3. Rivers, T. M.: Vaccine for Poliomyelitis, correspondence, J. A. M. A. **151**: 1224 (April 4) 1953.

4. Salk, J. E.: Recent Studies on Immunization Against Poliomyelitis, Pediatrics **12**: 471-482 (Nov.) 1953.

5. Bodian, D.; Morgan, I. M., and Howe, H. A.: Differentiation of Types of Poliomyelitis Viruses: III. The Grouping of 14 Strains into 3 Basic Immunological Types, Am. J. Hyg. **49**: 234-245 (March) 1949.

6. Committee on Typing of the National Foundation for Infantile Paralysis: Immunologic Classification of Poliomyelitis Viruses, Am. J. Hyg. **54**: 191-274 (Sept.) 1951.

7. Enders, J. F.; Weller, T. H., and Robbins, F. C.: Cultivation of the Lansing Strain of Poliomyelitis Virus in Cultures of Various Human Embryonic Tissues, Science **109**: 85-87 (Jan. 28) 1949.

8. Horstmann, D. M.: Poliomyelitis Virus in Blood of Orally Infected Monkeys and Chimpanzees, Proc. Soc. Exper. Biol. & Med. **79**: 417-419 (March) 1952.

9. Bodian, D.: Reconsideration of the Pathogenesis of Poliomyelitis, Am. J. Hyg. **55**: 414-438 (May) 1952; Bodian, D.: Experimental Studies on Passive Immunization Against Poliomyelitis: II. The Prophylactic Effect of Human Gamma Globulin on Paralytic Poliomyelitis in Cynomolgus Monkeys After Virus Feeding, Am. J. Hyg. **56**: 78-89 (July) 1952.

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Hammon established that poliomyelitis antibodies, passively transferred to human subjects by means of gamma globulin inoculations, temporarily enhanced protection against the paralytic form of the disease.[10]

These fruitful explorations led medical authorities serving on National Foundation advisory committees to recommend, in the fall of 1953, that an extensive field trial of the vaccine developed by Dr. Salk be conducted. In the past, other vaccine and immunizing agents had been introduced into general use on less substantial evidence of their effectiveness. Some, even after years of popular acceptance, have failed to demonstrate measurable evidence of efficacy. Others, through trial and error and the expenditure of considerable time, effort, and money had been modified and improved and had gradually established their usefulness in the prevention of acute communicable disease. It was assumed that with the resources of the National Foundation and with the widespread public concern for those afflicted with poliomyelitis a field trial applying modern methods of clinical, immunologic, and epidemiological study could with unprecedented speed establish answers to many unanswered questions. Could the vaccine prepared in the research laboratory be reproduced consistently and uniformly by commercial manufacturers? Would neutralizing antibodies induced by the vaccine protect susceptible individuals against the paralytic forms of the disease under natural conditions of exposure? Would mass use be attended by untoward reactions comparable to the dangers of the disease itself? If such a vaccine was protective, would the immunity artificially induced be complete or partial? Would the strains of virus used in this vaccine induce protection against all strains responsible for the naturally occurring disease? Are the comparatively few individuals who develop paralytic poliomyelitis through natural exposure those who do not respond readily to artificial immunization?

Many additional questions were raised, but it was apparent that none could be conclusively answered without crucial studies conducted on a scale sufficient to obtain statistically valid evidence. Some questions, concerning, for example, the duration of protection, would require long-term study. Most questions, however, seemed capable of answer within a one-year undertaking. The following objectives were therefore established for the field trial: (1) to determine whether a formaldehyde-inactivated trivalent poliomyelitis vaccine would offer protection against naturally occurring paralytic poliomyelitis to a selected group of children during the poliomyelitis season next following vaccination, and if protection is provided, the degree of such protection; (2) to determine what, if any, levels of actively induced antibodies are associated with subsequent resistance to paralytic disease; and (3) to observe the nature and incidence of untoward reactions to the vaccine. In mid-November, 1953, the National Foundation announced that the field trial would be initiated prior to the 1954 poliomyelitis season. The program, under the over-all supervision of Dr. Hart E. Van Riper, medical director of the National Foundation, was to be guided by advisory groups drawn from the National Foundation's own committees on research and professional education and by other committees designated by the Association of State and Territorial Health Officers.

Three phases were established for the field trial. The first concerned the planning of the entire operation and included the preparation, by cooperating manufacturers of biological products, of the large amount of vaccine that was needed. This phase began to accelerate in the summer of 1953 and continued beyond the actual start of inoculations in the field in late April, 1954. The Connaught Laboratories of the University of Toronto, Toronto, Canada, was enlisted to develop mass-production methods for the cultivation of virus in high concentrations by using monkey kidney tissue culture techniques. A group of American manufacturers, with extensive experience in the preparation of vaccines, were then recruited to undertake inactivation of the virus and actual production of the vaccine. Five such manufacturers agreed to participate on a nonprofit basis in this phase of the program. Two—Parke, Davis & Company of Detroit and Eli Lilly & Company of Indianapolis—succeeded in overcoming the many production problems and in meeting the rigid safety requirements in time to permit the use of their vaccine in the actual inoculation phase of the field trial.

The second or operational phase of the field trial gained momentum in the early fall of 1953 and reached a maximum of intensity in late April, May, and June, 1954, when inoculations were given. Technically speaking, the third or evaluation phase might be considered as beginning with the submission of completed reports to the evaluation center. However, no sharp line can be drawn between field operations and evaluation. Initially, the National Foundation itself supervised and coordinated field activities but even as the test materials—vaccine and placebo—were being administered to children in the schools, Dr. Thomas Francis Jr., and his group at the poliomyelitis vaccine evaluation center at the University of Michigan, Ann Arbor, assumed responsibility for supervision of the follow-up of those taking part in the trial and for collection and collation of case reports and other data essential to the preparation of the evaluation report.

Dr. Francis has previously presented summary findings of his evaluation study.[11] The decision to enlist Dr. Francis and to establish the evaluation center was predicated on the unquestioned need for an objective, independent evaluation of the vaccine. That this has been achieved is abundantly clear to all who have examined the summary report. Francis's report stands not only as a remarkable tribute to Dr. Francis and his immediate staff but also to literally thousands of practicing physicians, nurses, physical therapists, public health and school personnel, workers in collaborating laboratories, and the general public who cooperated in and contributed to its preparation.

10. Hammon, W. M.; Coriell, L. L., and Stokes, J., Jr.: Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis, J. A. M. A. **150**: 739-760 (Oct. 25) 1952.

11. Francis, T., Jr., and others: Evaluation of 1954 Field Trial of Poliomyelitis Vaccine: Summary Report, Am. J. Pub. Health **45**: 1-63 (May, pt. 2) 1955.

DESIGN OF STUDY

From the very beginning of the field trial it was recognized that a study of considerable size would be necessary if the effectiveness of the vaccine was to be measured. As is well known, the risk of poliomyelitis attack has been extremely small as compared with many other disease entities. During the 10-year period 1943-1952 national poliomyelitis case rates averaged only 18.5 per 100,000 population. Moreover, interannual variations in incidence in the United States have ranged during the last 15 years from a low of 3.1 in 1942 to a high of 37.2 in 1952 (fig. 1). The unpredictability of epidemic poliomyelitis in any given community in any given year is also well recognized. Because of these and other known epidemiological characteristics of the disease, a decision was reached to conduct the field trial on a nationwide basis, provided the cooperation and assistance of state and local authorities and of the public could be obtained. Communities would be selected according to geographical and socioeconomic factors so as to provide a representative cross section of the United States population. It was also agreed that preference would be given to communities where the maximum number of cases might be anticipated during the study year and to those communities where health and educational resources would permit the satisfactory conduct of the trial.

Early in the planning of the field trial, sharply divergent views were expressed in the selection of a control population against which the effect of the vaccine on those inoculated would be measured. Some held that the effectiveness of the vaccine could be measured only if a control population identical in all respects except for vaccination, and matched individual for individual with those immunized, was available. To meet these requirements it would be necessary to inoculate one-half of the study population with the vaccine and the other

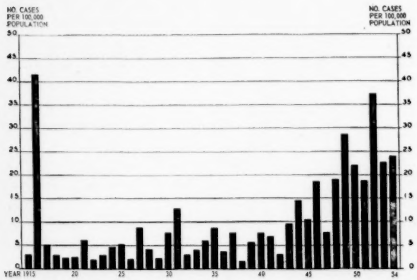

Fig. 1.—Reported poliomyelitis cases per 100,000 population in the United States, 1915-1954. The population was estimated in midyear by the Bureau of the Census. Data for 1954 were provisional. All data were taken from the U. S. Public Health Service.

with an inert material or one known to have no effect on the occurrence of paralytic poliomyelitis. In addition, the identity of the inoculated solutions would be masked by coded designations to be deciphered only after all observations had been completed and final analysis of results was in process. The difficulties inherent in carrying out such a placebo control study were acknowledged, but the proponents of this plan were confident that the advantages in terms of objectivity and ease of analysis far outweighed its disadvantages.

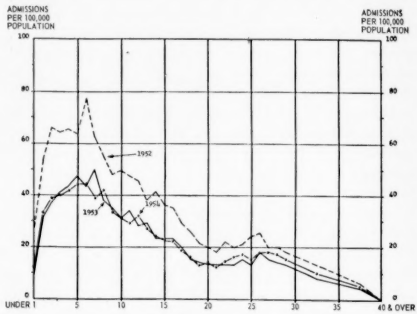

Fig. 2.—Poliomyelitis age specific acute admission rates per 100,000 population for 1952, 1953, and 1954. Population estimates are for mid-1952, mid-1953, and mid-1954. The 1952 rates are based on 35,882 notices of original acute admissions received July 20, 1952, through Jan. 31, 1953. The 1953 rates are based on 23,698 notices of original acute admissions received January through December, 1953. The 1954 rates are based on 24,950 notices of original acute admissions received January through December, 1954.

An observed control study was advanced by others as more desirable since its administration was far simpler. This plan would offer vaccine to all who volunteered to receive it. In the opinion of its proponents the effectiveness of the vaccine could be measured by comparing the incidence of paralytic poliomyelitis in those inoculated with that experienced by individuals of the same or comparable ages under similar conditions of exposure. Those proposing this plan of study discounted the likelihood of differences in attack rates arising purely as the result of selection of vaccinated and unvaccinated subjects or that unintentional bias might occur in the recording of illness in the two groups. Both plans of study were adopted; the choice of a placebo control study or an observed control study was left to the discretion of the responsible health officer of each state. Subsequent studies have indicated some of the selective factors that might affect the incidence of paralytic poliomyelitis in inoculated as opposed to observed control children.[12]

DETERMINATION OF COMPOSITION AND SIZE OF STUDY POPULATION

Since the degree of effectiveness of the vaccine was itself at test and since no reliable prediction of poliomyelitis incidence in the study population during the study period could be made, it was most imperative that the composition and size of the study group enhance the probability of statistically valid observations. On the other hand, time available for inoculations, limited supply of vaccine, and other factors exerted restrictions on the scope of the project. Although the age distribution of poliomyelitis has changed in the United

12. Clausen, J. A.; Seidenfeld, M. A., and Deasy, L. C.: Parent Attitudes Toward Participation of Their Children in Polio Vaccine Trials, Am. J. Pub. Health 44: 1526-1536 (Dec.) 1954. Francis,[11] pp. 13-14.

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States in recent years, it remains essentially a childhood disease. Almost 75% of reported cases occur under age 20 and over 50% in children under 10. The peak ages of clinically diagnosed poliomyelitis occur in the years immediately before and after entrance into primary school (fig. 2). This fact and the accessibility of school children in organized groups for vaccination determined the selection of children enrolled in the first three grades of primary school as the study population. Enrollment in these classes roughly corresponds with the age band 6 through 9 in which, on a national basis, at least one out of five of all reported cases might be expected to occur.

In addition, it was possible, utilizing the annual incidence rates of reported poliomyelitis for the United States, to estimate, on theoretical grounds at least, the probable minimum size of the study population required to give statistically valid results. Based on such analyses, it could be anticipated that if in the field trial areas a low incidence rate of paralytic poliomyelitis was encountered and the vaccine were only 50% effective, it might be necessary to vaccinate almost 700,000 children (and observe an equal number of controls) before valid findings could be obtained. If on the other hand, the vaccine should prove 80% or more effective and an "average" poliomyelitis year occur, a high level of certainty of the results could be derived from a study of fewer than 100,000 subjects equally divided between vaccinated and controls. A conservative approach dictated that a practical goal be set for the inoculation of between 500,000 and a million children.

TABLE 1.—*Poliomyelitis Crude Case Rates, by Size of County, 1948-1952*

Population Class, Thousands	No. of Counties	1950 Total Population, Millions	Reported Poliomyelitis Cases, 1948-1952		
			Total	Av. Annual No.	Av. Annual Rate per 100,000
Total, all counties	3,103 *	150.7	189,672	37,814	25.1
Under 50	2,608	47.6	65,289	13,058	27.4
50 and over	493 †	103.1	123,783	24,757	24.0
50 but less than 200	377	35.1	46,033	9,207	26.2
200 and over	116 †	67.9	77,750	15,550	22.9

* Includes 3,070 counties, 29 independent cities, the District of Columbia, and parts of Yellowstone Park in Idaho, Montana, and Wyoming.
† Includes District of Columbia, Baltimore, and St. Louis; excludes the cities of Norfolk and Richmond, Va.

SELECTION OF FIELD TRIAL AREAS

Earlier studies [13] cast doubt upon the possibility of selecting specific areas that might be expected to experience epidemic conditions during the field trial. On the other hand, the observations of Benjamin and Logan in England and Wales [14] offered encouragement that a group of areas with high prevalence in the past might yield higher-than-average attack rates in a subsequent year. In a report awaiting publication Stickle [15] confirmed these findings in studying poliomyelitis incidence in the more than 3,100 counties in the United States. Summarizing Stickle's findings, it became apparent that counties with a population of 50,000 to 200,000 experienced a significantly higher average annual attack rate than those with a population of over 200,000. Interestingly and consistently the recorded incidence of reported poliomyelitis is highest in counties with populations under 50,000 and yet, in general, it was necessary to omit these smaller jurisdictions from further consideration (table 1). Public health and medical resources requisite for the trial were less readily available in the smaller areas. Further analyses indicated that intercounty variability in case rates was more than three times that of year-to-year variance within counties and that counties with the highest average attack rates have, in the aggregate, a substantially higher than average attack rate one and two years later.

On the basis of such analyses, it seemed justified to recommend the participation of those counties of 50,000 to 200,000 population reporting the highest average attack rates during the five year interval 1948-1952, the latest period for which data were available. This preliminary method of selection did not exclude some larger and some smaller counties where it seemed both desirable and feasible to include such areas. In the extensive discussions that followed, several supplementary criteria for selection were developed. For example, preference was given to areas with well-organized health services capable of conducting effectively the operational and follow-up phases of the field trial, and where the interest and cooperation of local health and school authorities and the willingness of parents to request participation of their children in the test were overtly manifest. One additional criterion was important in the final selection of field trial communities. Areas experiencing significant outbreaks before the start of inoculations were to be excluded. This was considered desirable in order to avoid, as far as possible, any fortuitous association of inoculations with the onset of cases.

The final result of these considerations was the joint selection by the National Foundation and state health officers of 217 areas in 44 states. Placebo control studies were conducted in 91 areas in 11 states and observed control studies in 126 areas in 33 states. Before inoculations were begun in late April, 1954, the number of areas expected to participate was somewhat larger. However, Maryland, Arizona, and the District of Columbia withdrew because of inability to complete the inoculation program prior to the closing of schools. All three field trial areas in Georgia were excluded at the last moment because of the occurrence of cases of

13. Gilliam, A. G.; Hemphill, F. M., and Gerende, J. H.: Poliomyelitis Epidemic Recurrence in the Counties of the United States, 1932-1946, Pub. Health Rep. **64**: 1584-1595 (Dec. 9) 1949.

14. Benjamin, B., and Logan, W. P. D.: Geographical and Social Variations in the Incidence of Notified Poliomyelitis, Brit. J. Prev. & Social Med. **7**: 131-140 (July) 1953.

15. Stickle, G.: Statistical Criteria for the Selection of Poliomyelitis Vaccine Field Trial Areas, to be published.

paralytic poliomyelitis in the period immediately preceding inoculations. Minnesota authorities failed to sanction the program within that state in time to permit the necessary preparations. Because of interest in the program outside of the United States and the desire to add as many trial areas as time and materials would permit, 46 areas in three Canadian provinces—Alberta, Manitoba, and Nova Scotia—took part in the trial; two small areas in Finland also were included. In 1954, the areas included in the field trial in the United States experienced a reported case rate of 28.9 per 100,000 population, which was 26% higher than the rate in nontrial areas. Thus the criteria for the selection of participating trial areas actually fulfilled expectations in maximizing the number of cases in the test population.

ORGANIZATION AND ADMINISTRATION OF FIELD ACTIVITIES

It was apparent from the outset that large numbers of individuals with varying professional skills and other competences were needed if the test was to be successful. The majority of these individuals were volunteers recruited in the local field trial areas. It is estimated that more than 300,000 persons — including physicians, nurses, school teachers, public health and school officials, and community volunteers recruited by National Foundation chapters and by other civic, fraternal, or service organizations—cooperated in this extraordinary medical undertaking. Glasser has already summarized in an able manner how volunteers were recruited and effectively utilized in many of the community phases of the field trial.[16] Organization in each community centered around the schools where children who were to take part in the field trial were enrolled. Classroom teachers and volunteers shared in the school room census and registration of the study population, in the handling of parental request forms, in the basic education and preparation of children and parents for the test, and in the guidance of children to and from the vaccination clinics. For the most part, inoculation of children took place in school clinics; however, where the number in a given school was small, or where it was otherwise advantageous to do so, larger and centralized clinics were held elsewhere in the community. Coordination of activities in the schools was channeled through the school principal to the local health officer. In the absence of a local health officer, a qualified practicing physician served as the director of the local field trial program. It was the responsibility of the local director to enlist local interest and support for the program, to recruit the necessary physicians and other professional staff, and, with the aid of volunteers supplied by the local chapter of the National Foundation, to attend to the infinite number of details required by the program.

Within each state, the state health officer assumed over-all responsibility for the program. Participation in the field trial was, in general, predicated upon his prior consultation with state educational authorities, the state medical society, and such local groups in the prospective field trial areas as might be indicated. The state office staffs of the National Foundation and its regional representatives were placed at the disposal of state health departments to assist them in the many specialized tasks required. Though freedom to adapt the program to established local practices was permitted, each state agreed that uniformity of procedures and forms would be maintained, the publicity regarding results of the vaccination study would not be made independently, and that analysis of the data collected would be left exclusively to the evaluation center. There was universal understanding at all operational levels that publication of the results of the trial would be made only by the evaluation center when, in the opinion of Dr. Francis and his advisors, such would be justified.

Within the National Foundation itself, only a small coordinating staff was assembled, for the most part drawn from the various operating departments of the headquarters office. Under the direction of Dr. Van Riper, this group served as staff for the various advisory committees and provided liaison with the laboratories and manufacturers engaged in the preparation of the vaccine. In addition, it collected and analyzed essential statistical data, assisted state health departments in the selection and preparation of communities for field operations, and prepared educational and instructional materials and record forms for use in the field. Other departments of the National Foundation, particularly those dealing with its 3,100 local chapters and with public relations, were also intimately involved in the program. A major function of the National Foundation was to develop the interest and support of professional groups in the health and education fields and of civic, fraternal, and service clubs.

STANDARDIZATION OF PROCEDURES

So that each state and community taking part in the field trial would complete each step in a standardized manner, a Manual of Suggested Procedures was prepared.[17] Addressed primarily to the local health officer, the manual outlined the basic principles and policies of the field trial, defined functions and responsibilities of those participating in it and explained the procedures to be followed in each community. In addition, it described the record forms, educational materials, and supplies to be furnished by the National Foundation to each community. Supplements to the manual, in the form of operational memorandums, were also prepared so that physicians in charge of vaccination clinics, school principals, classroom teachers, clinic recorders, and others would have available to them relatively brief check lists of their tasks and assignments. As vaccinations proceeded, Dr. Francis issued a series of memorandums specifying the manner in which all records were to be handled. These memorandums also outlined the steps to be followed in the identification, study, reporting, and follow-up of each illness occurring in members of the study population, whether in a vaccinated child or not. A regular channel of communication was maintained between the evaluation center and the responsible health officers in each field trial area. Special effort was made to acquaint those

16. Glasser, M.: M Day for Polio, Adult Leadership 3:5-7 (Sept.) 1954.

17. Manual of Suggested Procedures for the Conduct of the Vaccine Field Trial in 1954, New York, National Foundation for Infantile Paralysis (March) 1954.

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with administrative responsibilities in the study areas with need for completeness, accuracy, and uniformity of all records that were to be forwarded to the evaluation center and ultimately provide the data essential to an objective appraisal of the vaccine.

RECORD KEEPING AND IDENTIFICATION OF THE STUDY POPULATION

All children enrolled in the first, second, and third grades of public, private, and parochial schools in the 217 field trial areas comprised the study population. Only by enumerating all members of this study population was it possible to determine accurately whether an individual experiencing poliomyelitis during the period of investigation belonged in the vaccinated or control groups and to calculate attack rates for the different categories of the study population. This basic enumeration was accomplished by use of registration schedules (form FT-3) that were completed for each of the three grades in every participating school. Each sheet and line was numbered uniquely, permitting permanent identification of each child by name, address, school, grade date of birth, sex, race, previous history of poliomyelitis, and presence or absence of muscular disability. These schedules were completed in the early preparatory phase of the trial; subsequent entry of additional information pertaining to inoculation and the collection of serologic specimens was made on the registration schedules. Participation in the field trial was voluntary; no child received inoculation, vaccine or placebo (solution 199), unless a parent so requested in writing. Permission was also sought for the collection of blood specimens for antibody determinations, if needed. The parents of each child in the study population received a printed parental request form (forms FT-1 and FT-2) through which they might request participation of their child in the field trial. Return of a signed form was no guarantee that the child would be inoculated with the vaccine. A surprisingly high proportion of parents, over 50%, asked that their children be included in whatever measures, inoculations, and/or collection of blood specimens, were decided on for them.

A vaccination record (form FT-4) was filled out for each child who received an inoculation or from whom blood was taken. It recorded the date of each of the three intramuscular inoculations of 1 cc. each at 0, 1, and 5 weeks, respectively, the lot or code number of the material given, the name of the physician giving the inoculation, and the dates blood specimens, if any, were drawn. Space was provided for recording any evidence of reactions. If the series of inoculations was not completed, the reason was stated. Information on the vaccination record was transcribed to the registration schedule, thereby permitting a check for accuracy and inconsistencies. Registration schedules and vaccination records were prepared in triplicate. They were edited locally and the first two copies sent to the state health department. Then, after review, the original copies were forwarded to the evaluation center for processing.

Collection of Blood Specimens.—Two other elements of the early field operations deserve mention. One involved the collection of blood specimens for neutralizing antibody determinations and the other the observation of vaccinated children and suitable controls for the occurrence of any untoward reactions that might be associated with the vaccine. The field trial offered an unusual opportunity to extend the earlier and limited observations of Salk with respect to the antibody response of human beings to the vaccine. After careful consideration, it was decided that three serial samples of blood would be sought from at least 2% of both vaccinated children and controls. These samples were collected at the time of initial inoculation, two weeks after the third inoculation and again at the conclusion of the poliomyelitis season, that is, approximately six months later. Almost 42,000 samples were collected at the first bleeding, over 34,000 at the second, and approximately the same number at the third. These and the following figures vary slightly from those appearing in Dr. Francis's summary report.[11] The data presented here are based upon preliminary tabulations submitted from the field to the National Foundation by state health officers; the records utilized and reported by Dr. Francis were subject to extensive editing and retabulation after the original records were submitted to the evaluation center.

At the time this plan was developed, only a few laboratories were in a position to undertake studies on the scale projected and only a small number had had experience in the extensive serologic tests contemplated. Nevertheless, 28 laboratories widely distributed geographically were recruited in a brief period of time to handle this vital phase of the investigation. In addition these laboratories participated in the equally important task of serologic study of and virus isolation from cases occurring in the study population.

Observation of Untoward Reactions.—An analysis of the incidence and nature of reactions associated with the vaccine was an integral part of the field trial. Between May 16, 1953, and March 9, 1954, Dr. Salk had inoculated 5,320 individuals with vaccine prepared in his own laboratory without causing any recognizable untoward effects upon the recipients, many of whom had received several inoculations. In addition, in the period immediately preceding the field trial, Dr. Salk had administered the commercially produced vaccine to be utilized in the field trial to 7,507 children. Of these, 3,097 had been observed for more than 21 days and 3,443 had been inoculated with vaccine at an earlier date. Again, no reactions were encountered with the single exception of transient urticaria in a child reported to be sensitive to penicillin. Some concern, however, was expressed lest nephrotoxic reactions, associated with the minute quantities of kidney tissue protein present in the vaccine, or Rh sensitization related to the inoculation of material containing minute quantities of monkey kidney, might represent genuine dangers to the mass use of the vaccine. Kumm [18] has summarized the careful investigations of such possible reactions that preceded the initiation of the field trial. Additional study of these and other possible untoward effects during the field trial was approached in several ways. The vaccination record made provision for the recording of reactions, and the

18. Kumm, H. W.: The Present Status of Vaccines for the Prophylaxis of Poliomyelitis, Illinois M. J. **106**: 13-19 (July) 1954.

manual of suggested procedures emphasized the need to record any untoward effects that appeared related to or coincidental with the administration of the vaccine. Specific instructions from the evaluation center requested notification by phone of any circumstances of significant severity that might be related to inoculations. In addition, special studies of absenteeism in schools and their causes were undertaken, and further laboratory and clinical investigations of the identifiable elements contained in the vaccine were carried out.

FIELD OPERATIONS

Initially, the time table established anticipated that inoculations in the field would begin in early February and continue through May, with the program starting in southern states, where the seasonal rise is usually first to appear, and proceeding northward. It was clearly understood, however, that inoculations would not begin until (1) there were assurances that sufficient vaccine would be available to permit a reasonable measurement of its effectiveness, (2) safety and sterility tests of a predetermined and exhaustive nature had been carried out independently on each lot of vaccine by three laboratories—by the manufacturers, by Dr. Salk, and by the Laboratory of Biologics Control of the National Institutes of Health, and (3) Dr. Salk had extended his preliminary pilot study to a minimum of 5,000 human subjects. In addition, the antigenicity of each lot of vaccine produced by manufacturers for use in the field trial would be titrated by Dr. Salk against the response he had obtained with material produced in his own laboratory.

These rigid though essential prerequisites, established by the vaccine advisory committee of the National Foundation, were met on April 25, 1954. This committee then recommended that the nationwide field trial proceed.[19] At that time the U. S. Public Health Service made the following statement: "We believe that the judgment of the Vaccine Advisory Committee is sound and that the National Foundation for Infantile Paralysis is justified in proceeding according to the Committee's recommendations." So that the medical profession would be kept fully informed concerning the background of the field trial and developments as they occurred, periodic releases were prepared for publication in national, state, and local medical journals. Shortly before the actual start of inoculations, each practicing physician in the country received through the mail a special preprint of an article on vaccination against poliomyelitis prepared by Dr. Van Riper.[20]

On April 26, 1954, the first series of inoculations were begun. Altogether, 653,793 individuals in a study population of 1,831,702 children in the United States received first inoculations. One week later 640,668 children began receiving their second inoculations, and five weeks later, 629,063 or over 96% who had received their first began to receive their third inoculations. Because of different starting dates in many of the field trial areas, the administration of vaccine and the collection of the first two blood samples in the 217 field trial areas in the United States continued to about mid-June. Because of later starting dates, this phase of the program continued in Canada and Finland somewhat longer (table 2). In placebo control areas the study required the giving of three matched inoculations of coded material over a period of five weeks to children in the first three grades of school. In fewer than 0.2% of the 421,031 children inoculated did a child receive a mixed series of vaccine and placebo. In observed control areas inoculations were given only to children in the second grade, and 232,762 were given vaccine in this segment of the study population. The negligible amount of confusion and recording errors observed during the inoculation phase can be attributed to the diligence of all those concerned with the field trial and to the supervision given by the evaluation center. During the vaccination period April 26 to June 15, personal visits were made by evaluation center staff to 32 of the 44 participating states.

TABLE 2.—*Preliminary Tabulation of Field Trial Study Population*

Study Areas, by Type of Control	Enrollment, Grades 1-3	No. Signed Parental Requests Received	Inoculations				Bleedings Completed		
			1st	2nd	3rd	3rd/1st, %	1st	2nd	3rd
All reporting areas (265)	1,905,124	977,286	700,742	686,478	672,443	96.0	41,924	34,120	33,772
Placebo control areas (139)	823,424	477,036	467,980	456,895	449,703	96.1	16,154	13,879	13,423
Observed control areas (126)	1,081,700	500,250	232,762	229,583	222,650	95.7	25,770	20,241	20,349
U. S. reporting areas (217)	1,831,702	947,005	653,793	640,668	629,063	96.2	40,273	32,818	33,193
U. S. placebo control areas (91)	750,002	446,755	421,031	411,085	406,413	96.5	14,503	12,577	12,844
U. S. observed control areas (126)	1,081,700	500,250	232,762	229,583	222,650	95.7	25,770	20,241	20,349
Canada and Finland reporting areas (48) (all placebo)	73,422	30,281	46,949	45,810	43,380	92.4	1,651	1,302	579

OBSERVATIONAL PHASE AND FOLLOW-UP PROCEDURES

A crucial element in the field trial was, of course, to determine the occurrence of poliomyelitis in members of the study population. This required the identification of all possible cases; the establishment of correct diagnosis by clinical, epidemiological, and laboratory study; accurate and complete recording of all relevant data in a systematic manner; and the transmission of all required information to the evaluation center at Ann Arbor. The primary responsibility for this fell on practicing physicians in local communities, particularly in the field trial areas, but in other localities as well. Local health officers and, in many states, the staff of the state health departments played an equally vital role in arranging for or actually participating in each of the steps

19. Poliomyelitis Vaccine Types 1, 2, and 3: Recommendations of Vaccine Advisory Committee of National Foundation for Infantile Paralysis and Statement of United States Public Health Service, New York, National Foundation for Infantile Paralysis (April) 1954.

20. Van Riper, H. E.: Vaccination Against Poliomyelitis, GP **9**: 59-62 (April) 1954.

essential to the identification, reporting, and investigation of cases. To reduce the need for discrimination locally and to encourage completeness of reporting and uniformity of procedure, a simple plan was devised by the evaluation center. All illnesses arising in any child enrolled in the first, second, or third grade in the spring term in schools located in the field trial areas, whether the child was inoculated or not, were to be investigated. Every case—paralytic, nonparalytic, suspected, or doubtful—was to be reported to the evaluation center and subjected to the same degree of study.

The lucid description given in Dr. Francis' summary report of the record forms, systematic checks and counterchecks, the use of diagnostic consultants and specially trained physical therapists for muscle grading examinations, and the availability of laboratory services and other follow-up procedures makes it unnecessary to review in detail at this time each of the precise steps taken in this phase of the field trial. It is now apparent that the information on 1,103 cases sent to the vaccine evaluation center from May 1 to Dec. 31, 1954, represented as complete a record of poliomyelitis experience in the field trial population during the study period as human ingenuity and competence could devise.

SUMMARY

That an extensive field trial of a poliomyelitis vaccine has been conducted by the National Foundation and many cooperating individuals and agencies has been widely publicized. It is almost universally known that this basically medical test—unprecedented in its objectives, its magnitude, and its scope—has been highly successful, and there is now available to the public a safe and simple measure offering 60 to 90% protection against paralytic poliomyelitis. A few days after the announcement of the results of Dr. Francis's evaluation in Ann Arbor, Mich., on April 12, 1955, a Gallup poll indicated that 96% of all people interviewed in the national sample and 98% of all people with children under the age of 15 had heard about the vaccine. The report indicated that more people knew about the vaccine than had known of almost any news event on which a public opinion poll had ever been taken.[21]

What has been less readily recognized is the step-by-step and painstaking labor that has made our present confidence of mastery over this disease possible. For more than 50 years scientists throughout the world have slowly accumulated better understanding of each of the many phases of this disease, its clinical and epidemiological characteristics, its etiology, its pathogenesis, and its immunologic manifestations. The seemingly disparate elements of a highly complex mosaic began to fit together into recognizable form only when a coordinated attack on poliomyelitis, sponsored primarily by the National Foundation for Infantile Paralysis was launched 17 years ago. Since 1948, the progress achieved by this frontal attack has been rapid and dramatic, and it can be suggested that the preliminary planning for the crucial experiment comprising the 1954 vaccine field trial actually goes back that far. It has been stated by competent authority that the uniqueness of a safe, potent, and effective poliomyelitis vaccine, available for widespread use, is in large measure inherent in the circumstances surrounding it rather than in the preparation itself. For the first time in medical history, a vaccine has been developed as a result of a publicly supported program of medical research.

Uniqueness, also, is intrinsic in the decision of the scientific advisors of the National Foundation for Infantile Paralysis to determine precisely the validity of the vaccine's protective effect. Despite the fact that the vaccine's safety and ability to stimulate the production of specific antibodies had already been established by extensive laboratory, animal, and human being tests, the decision was made to establish its protective effects in a statistically significant group of children under natural conditions of exposure before it was made generally available to the medical profession and to the public. It is possible to reflect now how sound this decision was. Also, unprecedented in medical and scientific history has been the demonstration that literally hundreds of thousands of volunteers—physicians, nurses, physical therapists, laboratory workers, public health and school personnel, and the general public—can be effectively mobilized in a truly scientific endeavor. This achievement required an unusual degree of foresight and imagination, meticulous and deliberate planning and organization at each stage of development of the program, and, finally, the unfaltering confidence of the American public who have made the National Foundation for Infantile Paralysis and its program possible. In the last analysis the field trial has not been an end in itself; it is merely another step, though a great one, in the advance of human understanding of and control over paralytic poliomyelitis.

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21. American Institute of Public Opinion: Personal communication to the author.

Accidental Death from Electric Current.—The death rate from accidents involving electric current has decreased over the years. At present, such accidents take about 1,000 lives annually in the United States, or 7 per million population, whereas a quarter century ago the corresponding death rate was 9 per million. Fatalities due to electric current show a distinct seasonal pattern, beginning to increase in the spring and reaching a peak in the summer; more than two fifths of the deaths each year occur in June, July, and August. The higher mortality in summer results largely from increased activity in the repair and extension of electric lines and from the generally greater amount of outdoor work which brings men in accidental contact with electric lines. Moreover, when the body is wet with perspiration, as is often the case in warm weather, its resistance to electric shock is lowered. About 95% of the fatal accidents caused by electric current in the United States occur among males, reflecting largely the effect of occupational hazards. It is not surprising, therefore, that the victims are concentrated principally in the main working ages of life. . . . Somewhat over one fifth of all the males killed by electric current in 1951-1952 sustained their injuries on industrial premises—electric light and power plants, factories, workshops, and similar places. . . . Hazards on the farm have been responsible for an appreciable loss of life from electric shock; the toll was 181 (177 of them males) in 1951-1952. For the most part these fatal accidents involved farm production equipment, such as irrigation pumps, machinery, and electric fences. . . . Accidents in the home accounted for one sixth of the deaths due to electric current among males and for about four fifths of those among females in 1951-1952.—Accidental Death from Electric Current, *Statistical Bulletin Metropolitan Life Insurance Company*, May, 1955.

EVALUATION OF THE 1954 POLIOMYELITIS VACCINE FIELD TRIAL

FURTHER STUDIES OF RESULTS DETERMINING THE EFFECTIVENESS OF POLIOMYELITIS VACCINE (SALK) IN PREVENTING PARALYTIC POLIOMYELITIS

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The purpose of the poliomyelitis vaccine evaluation program in the field trial of 1954 was to seek a measure of the prophylactic effect of the preparations of vaccine to be used, the only assumptions being that the experimental background was sound and that the vaccine was to be antigenic and noninfectious. The undertaking meant the acceptance of a public and scientific trust to provide, so far as possible, an objective analysis and unprejudiced appraisal of data obtained from numerous study areas. It must be fully realized that the evaluation program was not a tightly knit operation carried on by a single group of investigators. Rather, it was a widespread series of investigations that the vaccine evaluation center at the University of Michigan sought to integrate by obtaining uniform acceptance of instructions and procedures and, thus, to maintain uniformity of understanding and performance and completeness and accuracy of investigation and report. In effect, then, the center served as the executive agency for a study dependent upon the willingness, interest, and cooperation of the local medical profession, both administrative and practicing, and of their affiliated personnel. But, in addition, there was the extended network of virus laboratories, geographically distributed, to aid in the specific diagnosis of reported cases; a large number of specially oriented physical therapists who would make detailed examinations of the muscular status of each patient in assigned study areas. Beyond this was the great background of public interest leading to their voluntary participation in an investigation that was, in the end, completely dependent upon their support.[1]

All data from all areas were transmitted to the center on forms devised for the specific step. Throughout the study period the major effort of the staff of the center was concentrated on getting the necessary information from the different agencies responsible for the actual work at the local level. All possible means were used to eliminate delays, inaccuracies, or omissions in the requisite reports, with the result that a high degree of completeness was finally attained.

STUDY PLANS

The evaluation program embraced two distinct plans. The plan originally announced by the National Foundation for Infantile Paralysis was to vaccinate all children in the second grade of school whose parents requested it, while all the children of the first and third grades were to be kept under observation as controls for the vaccinated children. The ease of carrying out vaccination under such conditions recommends the procedure, but it presents possible disadvantages in the evaluation by the ready opportunity for the introduction of bias at any stage in the diagnosis and investigation of cases. The vaccinated persons are those who specifically volunteer; the controls comprise both those who might volunteer and those who would not. The age groups do not correspond, although the first and third grades bridge the second grade in this respect. It can readily be determined whether a child was vaccinated or not, and that knowledge could influence subsequent consideration. Table 1 presents the number of participants in the "observed study areas."

TABLE 1.—*Distribution of Study Population, by Participation Status and Vaccination Status—Observed Areas*

Study Population	No.	% of 2nd Grade	% of Total Population
All grades			
Total	1,080,680	....	100.0
Requests	567,210	....	52.5
2nd grade (requests)	245,895	69.2	22.8
Complete vaccinations	221,998	62.4	20.5
Incomplete vaccinations	9,904	2.8	0.9
Absent or withdrew	13,993	3.9	1.3
1st and 3rd grades (requests)	321,315	....	29.7
All grades			
Participation not requested	332,870	....	30.8
Participation not recorded	180,600	....	16.7

In order to achieve strict impartiality in the study of patients in test and control groups, the second plan of study was introduced. It comprised all children of the first, second, and third grades whose parents requested their participation, with a clear understanding that half would receive vaccine and the other half a placebo, while knowledge of the inoculum was available only by a code held at the evaluation center. Those who received the placebo were the controls and have been shown in all respects to be counterparts of the vaccinated children (table 2). Those who did not participate were not considered additional controls. The uninoculated persons were, however, to be followed in the same manner as the participants; it was also to be true of uninoculated persons in the second grade of observed areas. This was adopted to gain uniformity of investigative procedure without consideration of vaccination status and to avoid selective problems at the local level. But it should be emphasized that those not included as participants are not an integral part of the evaluation; they are a different population. Evidence that they are different was clearly supplied in a survey of the socioeconomic status and

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Read in the Panel Discussion on Prospects for the Control of Poliomyelitis before the Joint Meeting of the Section on Pediatrics and the Section on Preventive and Industrial Medicine and Public Health at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 7, 1955.

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

1. Francis, T., Jr., and others: Evaluation of the 1954 Field Trials of Poliomyelitis Vaccine: Summary Report, Am. J. Pub. Health 45:1-63 (May, pt. 2) 1955.

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the reaction to health problems among families of the placebo study areas. Numerous studies have indicated differences in antibody development and susceptibility to poliomyelitis between portions of populations of different socioeconomic levels, and the differences demonstrated in the survey indicated that the nonrequesting population might well be a more resistant group than the inoculated.

DATA REQUIRED FOR EVALUATION

The vaccination program was carried out between the end of April and mid-June. The first problem was that of collecting and verifying the basic information on each of the 1,829,996 children in the total study population. It included a record of the lot of material given in each inoculation to each child. These data were transferred to punched cards so that tables describing the population according to essential characteristics could be prepared. It was an extensive but essential task, since it provided the necessary identification of the vaccinated and control persons in whom the incidence of poliomyelitis would be investigated and the measurement of vaccine's effect would be made. In addition, from more than 40,000 children of the vaccinated and control groups samples of serum were obtained prior to the time of injection, together with serums taken two weeks after the clinics were completed and again five months later, and were to be tested in the respective laboratories. These records were also established and results received at the center. From them the distribution of antibody in this segment of the population in different parts of the country, the response to vaccine, the persistence of effect, and possibly information on the extent of natural exposure to poliomyelitis virus in the different areas during the study period as indicated by antibody changes could be determined.

TABLE 2.—*Distribution of Study Population, by Participation Status and Vaccination Status—Placebo Areas*

Study Population	No.	%
Total in grades 1, 2, and 3	749,236	100.0
Total requests to participate	455,474	60.8
Complete series of injections		
Vaccine	200,745	26.8
Placebo	201,229	26.9
Incomplete injections		
Vaccine	8,484	1.1
Placebo	8,577	1.1
Absent at first clinic or withdrew	36,439	4.9
Number not requesting participation	280,868	37.5
Participation status not recorded	12,894	1.7

The second phase in the evaluation was concerned with discovery and identification of all cases of poliomyelitis or suspected poliomyelitis in all children of the first, second, and third grades in the study areas. The various steps in the investigation of a case are: (1) physician's diagnosis—report to local health department; (2) telegraphic report to vaccine evaluation center; (3) action of local health department, including (*a*) clinicoepidemiological investigation and report to vaccine evaluation center, form FT-6, (*b*) collection and shipment of laboratory specimens (or by laboratory) and notice to vaccine evaluation center, form FT-9, and (*c*) notification of physical therapist; (4) first muscle evaluation by physical therapist (10 to 20 days) and physician's interpretation of patient's status, form FT-7; (5) collection of convalescent serum for laboratory, form FT-9; (6) second muscle evaluation by physical therapist (50 to 70 days) and physician's interpretation of patient's entire illness, form FT-8; (7) report of virus isolation, tests of antibody titer, laboratory diagnosis, form FT-10; (8) establishment and application of criteria for diagnosis of individual patient; and (9) integration of all data into final vaccine evaluation center diagnosis.

The criteria for diagnosis of poliomyelitis, for designation of a case as paralytic and its severity, and for the interpretation of laboratory results were carefully drawn. In this we had the continued help of an advisory committee comprised of expert clinicians, virologists, biostatisticians, epidemiologists, and administrators. The information concerning each case was carefully reviewed and the diagnostic classification made without knowledge of its vaccination status so that objectivity was readily maintained. Inevitably, difficulties in decision were encountered when results from different pieces of data were not in agreement, but the effort was made to follow a consistent plan of interpretation.

RESULTS

The study period was defined as the period from two weeks after the time of the third injections in an area to Dec. 31, 1954. The beginning was selected because it coincided generally with the time when second blood specimens were obtained for measurement of antigenic response to vaccine. During the study period there were 1,013 cases reported to be poliomyelitis or suspected poliomyelitis; 428 in the total study population of placebo areas and 585 in the total study population of observed areas. With the criteria employed, 67.6% were classified as paralytic, 17.6% as nonparalytic, and 14.8% as not poliomyelitis or doubtful. There was no major difference in distribution of diagnoses in the two populations.

Table 3 shows the cases distributed according to the various segments of the total populations involved. It must be emphasized again that the evaluation is limited to a comparison of incidence in the vaccinated and in the established controls. The nonparticipating portions of the populations, that is, those who specifically refused to participate, are not additional controls. That decision was firmly established well in advance of the tabulation of results. The data are presented only because they are available and for completeness of reporting. The cases and rates per 100,000 of specific population are listed. In the placebo control areas there was a total of 82 cases reported among the 200,745 vaccinated and 162 among the 201,229 who received a placebo. The corresponding rates are 41 and 81—a ratio of 1:2; however, 25 and 20 cases, respectively, were classified as not poliomyelitis or doubtful. Thus, when the cases accepted as poliomyelitis are compared, there are 57 and 142, respectively, with rates of 28 and 71, a ratio of 1:2.5. When these are subdivided into paralytic and nonparalytic groups, no dif-

ference is observed between the incidence of nonparalytic cases among vaccinated and control persons. The sole significant difference, then, resides in the cases classified as paralytic poliomyelitis; there were 33 in the vaccinated group and 3.5 times as many, 115, in the placebo control group. In the observed control study, the number of controls is 3.3 times that of the inoculated; hence, for comparison the rates must be used. Here, again, there is no significant difference between the rates in nonparalytic cases or between the doubtful and not poliomyelitis groups in the vaccinated and control patients. The rates for paralytic cases are, however, 17 and 46 respectively —a ratio of 1:2.7.

This possibility was an essential reason for establishing the strictly controlled placebo study. Moreover, the uninoculated—or refused—portion of the second grade in observed areas also had a lower rate than the designated controls who themselves were both "yes" and "no" participants. When the incidence rates in control and uninoculated groups combined are calculated for the placebo study and for the observed study, they are the same, 43.7 and 43.9 respectively. The differences disappear.

Lack of Evidence of Provocation or Infection from Vaccination.—It had been suggested that the placebo inoculations might exert some provocative influence toward paralytic poliomyelitis. Analysis of the data reveals no evidence of exaggerated incidence or localization of paralysis associated with inoculations. Further information is presented regarding the occurrence of poliomyelitis in the total study populations during the nine-week period from the beginning of vaccination to four weeks after the third injections in an area. There were 129 reported cases. As seen in tables 4 and 5, no distinctive difference in incidence in time of occurrence of cases appears in the vaccinated, placebo, or uninoculated groups of the placebo areas, or in the corresponding groups of the observed areas. The latter included many more southern states where poliomyelitis was already being reported at the time of vaccination, especially in Texas where half of the cases occurred (table

TABLE 3.—*Summary of Study Cases by Diagnostic Class and Vaccination Status, Rate per 100,000*

Study Group	Study Population	All Reported Cases		Poliomyelitis Cases						Doubtful or Not Poliomyelitis	
				Total		Paralytic		Nonparalytic			
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
All areas, total	1,829,916	1,013	55	863	47	685	37	178	10	150	8
Placebo areas, total	749,236	428	57	358	48	270	36	88	12	70	9
Vaccinated	200,745	82	41	57	28	33	16	24	12	25	12
Placebo	201,229	162	81	142	71	115	57	27	13	20	10
Not inoculated *	338,778	182	54	157	46	121	36	36	11	25	7
Incomplete vaccinations	8,484	2	24	2	24	1	12	1	12	..	..
Observed areas, total	1,080,680	585	54	505	47	415	38	90	8	80	7
Vaccinated	221,968	76	34	56	25	38	17	18	8	20	9
Controls †	725,173	439	61	391	54	330	46	61	8	48	6
2nd grade not inoculated	123,605	66	53	54	44	43	35	11	9	12	10
Incomplete vaccinations	9,904	4	40	4	40	4	40	..	..	..	..

* Includes 8,577 children who received one or two injections of placebo. † 1st and 3rd grade total population.

TABLE 4.—*Study Cases with Onset up to Nine Weeks from Date of First Inoculation, by Vaccination Status*—Placebo Areas*

	Total	Poliomyelitis Virus Recovered, Type			Negative Isolation	Other Virus Recovered	Not Collected or Not Done	No. of Wk. from Wk. of First Inoculation to Wk. of Onset									
		1	2	3				0	1	2	3	4	5	6	7	8	9
Vaccinates																	
Paralytic	2	..	..	..	2	..	..	..	..	..	..	..	..	1	..	1	..
Nonparalytic	1	..	..	..	..	1	..	..	..	..	..	..	..	..	1	..	..
Not poliomyelitis or doubtful	3	..	..	..	1	..	2	..	..	..	..	..	1	1	..	1	..
Placebo																	
Paralytic	4	..	..	2	2	..	..	..	..	..	..	1	1	..	..	2	..
Nonparalytic	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Not poliomyelitis or doubtful	3 †	..	..	..	1	..	2	..	..	..	1	..	1	..	..	1	..
Partial vaccinates																	
Paralytic	2	1	..	..	1	..	..	..	..	1	..	1 ‡	..	..	..	..	..
Nonparalytic	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Not poliomyelitis or doubtful	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
All other																	
Paralytic	8	1	..	2	1	..	4	..	..	1	1	..	1	1	..	3	1
Nonparalytic	4	..	..	1	3	..	..	..	..	..	..	..	1	..	2	1	..
Not poliomyelitis or doubtful	5	..	..	..	5	..	..	..	..	..	..	..	..	4	1	..	..

* Date of first inoculation in school used for uninoculated children. † Partial placebo, one case. ‡ Doubtful facial.

The lack of effect in nonparalytic cases may indicate that they include a sizable proportion of cases that in reality are not poliomyelitis or that vaccination did not prevent infection and minor degree of illness, although limiting the development of paralytic involvement. But it must also be pointed out that, with the criteria employed, only 15 to 17% of the cases remained in the nonparalytic category. The question has been asked why the incidence of paralytic cases is less in the uninoculated members of the population than in the placebo controls. One can only repeat that the populations receiving vaccine or placebo are strictly comparable in every characteristic; they are equal parts of one population, while those who refused participation are distinctly different.

6). The number of cases in the first and third grade controls and in the vaccinated group is directly proportionate to the population. The tables also contain the results of efforts to isolate virus from the reported cases. From the four cases of paralytic poliomyelitis among those receiving vaccine, partial or complete series, type 1 virus was recovered once; the others were negative. Poliomyelitis virus was recovered only once from vaccinated persons in the observed areas, a type 2. From half of the paralytic cases in the control group in which myelitis and negative virus studies. There were three instances of similar nature in the placebo group, three in the uninoculated of the placebo study areas, three in the controls, and one in the nonparticipating group of observed areas. There is, therefore, no indication of undue transmission of poliomyelitis virus from vaccinated persons in this period to other members of the household.

Distribution of Paralytic and Laboratory Confirmed Cases.—The subsequent analyses of case distribution were directed toward the combining of clinical and labo-

TABLE 5.—*Study Cases with Onset up to Nine Weeks from Date of First Inoculation, by Vaccination Status*—Observed Areas*

	Total	Poliomyelitis Virus Recovered, Type			Negative Isolation	Other Virus Recovered	Not Collected or Not Done	No. of Wk. from Wk. of First Inoculation to Wk. of Onset								
		1	2	3				0	1	2	3	4	5	6	7	8	9
Vaccinates																	
Paralytic	7	..	..	..	6	..	1	..	1	..	1	..	..	1	1	3	..
Nonparalytic	5	..	1	..	3	1	..	..	..	1	..	1	1	1	..	1	..
Not poliomyelitis or doubtful	6	..	..	..	4	..	2	..	..	..	2	..	..	1	2	1	..
Control																	
Paralytic	25	8	..	4	12	..	11	3	3	4	2	4	3	6	1	5	4
Nonparalytic	15	..	..	1	4	..	10	2	1	..	..	4	1	2	2	3	..
Not poliomyelitis or doubtful	9	..	..	..	8	..	1	1	2	..	1	1	..	..	1	2	1
Partial vaccinates																	
Paralytic	4	..	..	..	3	..	1	..	1	..	1	..	2	..	..	..	..
Nonparalytic	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Not poliomyelitis or doubtful	4	..	..	..	4	..	..	1	1	..	1	1	..	..	..	..	..
All other																	
Paralytic	5	1	..	1	2	..	1	..	1	..	..	1	..	..	3	..	..
Nonparalytic	5	..	..	..	2	..	3	1	1	..	..	1	1	..	..	1	..
Not poliomyelitis or doubtful	2	..	..	..	2	..	..	..	..	1	..	..	..	..	..	1	..

* Date of first inoculation in school used for uninoculated children.

TABLE 6.—*Study Cases with Onset up to Nine Weeks from Date of First Inoculation, by Vaccination Status*—Texas*

	Total †	Poliomyelitis Virus Recovered, Type			Negative Isolation	Not Collected or Not Done	No. of Wk. from Wk. of First Inoculation to Wk. of Onset								
		1	2	3			0	1	2	3	4	5	6	7	8	9
Vaccinates																
Paralytic	5	..	..	..	5	..	..	1	..	..	..	..	..	1	3	..
Nonparalytic	3	..	..	..	3	..	..	..	1	..	1	..	..	..	1	..
Not poliomyelitis or doubtful	2	..	..	..	2	..	..	..	..	1	..	..	..	1	..	..
Control																
Paralytic	16	5	..	2	6	3	..	1	..	2	2	2	4	1	2	2
Nonparalytic	10	..	..	..	2	8	2	1	..	..	..	1	2	1	3	..
Not poliomyelitis or doubtful	4	..	..	..	3	1	1	1	..	..	1	..	..	..	..	1
Partial vaccinates																
Paralytic	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Nonparalytic	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Not poliomyelitis or doubtful	1	..	..	..	1	..	..	..	..	..	1	..	..	..	..	..
All other																
Paralytic	1	1	..	..	..	..	..	..	..	..	..	..	..	1	..	..
Nonparalytic	2	..	..	..	..	2	..	..	..	..	1	1	..	..	..	..
Not poliomyelitis or doubtful	2	..	..	..	2	..	..	..	1	..	..	..	..	..	1	..

* Date of first inoculation in school used for uninoculated children. † No viruses other than the poliomyelitis virus were recovered.

tests were done, poliomyelitis virus was isolated: eight type 1 and four type 3.

There were only two instances of poliomyelitis in associates of vaccinated persons during this nine-week period. The study member in New York state received the third injection of vaccine on June 17; the sibling developed nonparalytic poliomyelitis 26 days later, and 2 days later the vaccinated child developed poliomyelitis with minimal paralytic signs; no virus was recovered. In Texas, a child received his third injection of vaccine on June 15, and 21 days later had the onset of mild bulbar poliomyelitis, but no virus was recovered. The sibling had his onset on the same day, with nonparalytic poliomyelitis and negative virus studies.

ratory data that enhance the reliability of diagnosis. A summary of these progessive stages with accompanying estimates of effectiveness in the two types of study are given in table 7. In the placebo areas there was a distinct trend for the differences in ratio between vaccinated and controls to increase as the severity of paralytic involvement increased. In spinal paralytic cases of minimal degrees of involvement the difference was only 2:1, suggesting that here, too, cases that were not specific poliomyelitis virus infections were included in these clinical classifications. In the more severe classes, however, the distinction became quite marked, emphasizing the possibility that the vaccine exhibited its major influ-

ence in preventing significant muscular impairment. The difference in rates for bulbospinal cases was pronounced and highly significant.

The same trend occurs among spinal paralytic cases in observed areas, but the difference between total bulbospinal rates is less, apparently owing to the lack of effect in cases with minimal paralytic ratings. The limited number of cases, however, can significantly limit the degree of numerical agreement in the two studies. Analysis of paralytic cases that were designated by virus isolation, serology, or virus in family associates as specific infections with the known types of poliomyelitis virus was then undertaken. This obviously reduces again the number of cases admitted to consideration. It is seen, however, that with these criteria, the estimated effect of vaccine was the same in spinal paralytic cases of both placebo and observed study areas. However, the discrepancy between the bulbospinal cases in the two studies persists.

Finally, the distribution was studied of all cases, paralytic and nonparalytic, from whom a specific poliomyelitis virus was isolated. In placebo areas an effectiveness of 68% was estimated against type 1, and 90% or more against types 2 and 3. In observed areas the trend was the same but lower. What, then, can be given as the effectiveness of vaccine? The calculations presented in the table appear to be valid estimates from the summarized data. Subsequent review has not revealed significant error. It is fully recognized that larger numbers would have created greater security, but the data obtained are unprejudiced appraisals. The strictly controlled placebo study provides the data in which there is greater confidence than those from the observed control study. In fact, the results from the observed areas would be more difficult to interpret if they had not followed the trend of those obtained in the placebo study. The lesser effect seen against type 1 virus is in accord with the lesser antigenic effect of a number of the preparations of vaccine measured against type 1 virus. But taking the composite results against laboratory confirmed cases of paralytic poliomyelitis an effectiveness of 80 to 90% was observed in the placebo study areas and 60 to 80% in observed study areas. It must be emphasized that the results presented apply to the circumstances in effect for the 1954 studies during which intensive efforts were made to obtain as complete and uniform data as conditions of study would permit.

There are questions arising from the data to which there is yet no ready answer. The incidence of paralytic cases in the 6-year-old group did not appear significantly different in vaccinated and controls of the placebo areas. It can only be pointed out at the present that when these cases were considered in terms of virus isolation, there were four cases of type 1 in each group, but there were no type 2 or type 3 cases in the vaccinated while one and five cases, respectively, occurred in the controls. Study of this problem is continuing.

SUMMARY

This review has been directed to a further summary of the report of the evaluation of the 1954 field trial of poliomyelitis vaccine. The data appear on further examination to retain their validity. Possible harmful effects of the poliomyelitis vaccine were not indicated by the data. Again, the definition of controls and the value of strictly controlled studies is emphasized. It is apparent that the medical profession at large needs further preparation for effective participation in the investigation of health problems in which their activities as physicians may contribute the essential data.

TABLE 7.—*Estimates of Effectiveness of Vaccine at Successive Stages of Analysis*

Diagnostic Classification	Placebo Study Areas: No. of Cases Vaccinated	Placebo Study Areas: No. of Cases Controls	Placebo Study Areas: Significance Level	Placebo Study Areas: % Effectiveness Estimate	Placebo Study Areas: % Effectiveness Lower Limit	Observed Study Areas: No. of Cases Vaccinated	Observed Study Areas: No. of Cases Controls	Observed Study Areas: Significance Level	Observed Study Areas: % Effectiveness Estimate	Observed Study Areas: % Effectiveness Lower Limit	Source of Data
Total cases reported *	82	162	<0.001	49	36	76	439	<0.001	44	32	Table 3
Total poliomyelitis	57	142	<0.001	60	49	56	391	<0.001	54	32	
All paralytic	33	115	<0.001	72	61	38	330	<0.001	62	51	
All nonparalytic †	24	27	NS	..	..	18	61	NS	..	..	
Paralytic-spinal	28	70	<0.001	60	39	20	199	<0.001	66	53	Tables 3*a*, *b* ‡
Bulbospinal	2	36	<0.001	94	81	15	100	<0.001	50	19	
Laboratory confirmed											
Spinal	8	45	<0.001	82	65	7	127	<0.001	83	64	Tables 5*a*, *b* ‡
Bulbospinal	2	23	<0.001	91	68	9	71	<0.01	60	23	
All virus positive											
Total	15	70	<0.001	80	65	20	210	<0.001	69	56	Tables 6*a*, *b* ‡
Type 1	13	39	<0.001	68	41	14	114	<0.001	62	33	
Type 2	0	6	<0.05	100	33	2	34	<0.01	80	33	
Type 3	2	25	<0.001	92	72	4	62	<0.001	78	47	

* Because of small numbers the bulbar and fatal cases are omitted. All fatal cases occurred in controls.
† The difference in distribution of nonparalytic cases is not significant at any stage of analysis.
‡ Francis and others.[1]

The Care of Cardiac Patients.—The pitfalls in the care of cardiacs are numerous, but mainly concern the original diagnosis of the case. Before a physician embarks on the treatment of a given patient with heart disease he must ask himself three questions: First, is organic heart disease present? Second, is there evidence of congestive failure or coronary failure? Finally, is there something peculiar about the problem that requires more than the ordinary type of treatment, such as some form of surgical operation (pericardial resection), or is it a reversible form of heart disease, such as beriberi or thyrotoxic heart disease? Only after these three questions are satisfactorily answered should the patient be placed on the customary program of digitalis, diuretics, etc. When ordinary congestive heart failure is present, and the physician is certain that it is not due to one of the causes amenable to or curable by surgery, the problem is generally well treated by the average physician.—S. A. Levine, M.D., Pitfalls in the Care of Cardiacs, *Annals of Internal Medicine*, June, 1955.

CONTROL OF POLIOMYELITIS THROUGH VACCINATION

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Recent progress in poliomyelitis research has culminated, after a decade of work, in the development of a useful vaccine [1] to combat paralysis. The vaccine is the first, and currently the only, control measure usable on a large scale that appears to provide substantial immunity against the paralytic form of this disease. Poliomyelitis is a nationwide health problem that has increased in size and significance in recent years. It is one of the few communicable diseases, in fact, that has shown a rise in both incidence and death rates in the United States during the past two decades. Nonetheless, the incidence of clinical poliomyelitis today is considerably less than that of many other infectious diseases.

In 1954, the third highest year of reported poliomyelitis incidence in United States history, 38,741 cases of poliomyelitis (including both paralytic and nonparalytic cases) were reported to the Public Health Service. In the same year there were about 50,000 reported cases of infectious hepatitis, 61,000 reported cases of whooping cough, 145,000 reported cases of streptococcic sore throat and scarlet fever, and 683,000 reported cases of measles. It must be remembered, however, that the cumulative total of individuals with residual paralysis from poliomyelitis mounts each year. About 75% of all cases of poliomyelitis in 1954 occurred in children 1 to 19 years of age, with peak incidence, for the country as a whole, among children 5 to 9. The age-specific incidence varies according to geographical area, however, and in recent years a definite shift to peak incidence in older children and adults has been observed in some parts of the country. In terms of morbidity and mortality, poliomyelitis ranks well below most diseases of childhood. It is, however, a significant public health problem because of: (*a*) its seasonal and epidemic nature, (*b*) its residual and permanent disabling effects, (*c*) the fear and dread it inspires in parents, and (*d*) the absence, until now, of effective control measures.

Infection with poliomyelitis virus is characterized by multiplication of virus in tissues of the gastrointestinal tract, with resultant shedding of virus in pharyngeal secretions and feces. At some stage in this infection there may be a transient viremia. In a small proportion of cases, the central nervous system may be invaded during the viremia. Classic symptoms of paralysis, therefore, develop only in a small proportion of the infections. Antiviral immune bodies that result from natural infection or from vaccination do not prevent subsequent infection of the gastrointestinal tract but act as a barrier during viremia to block invasion of the nervous system.

No practical measures for controlling the spread of poliomyelitis infection from person to person are known, but the poliomyelitis vaccine has been demonstrated to be effective in preventing the paralytic form of the disease. Gamma globulin, when used prior to the viremic stage of the disease, offers some short-lived protective effect by passive transfer of antibodies. Since the ratio of recognized cases to subclinical infections frequently approximates 1 to 100,[2] infection is widespread early in the course of poliomyelitis outbreaks. Thus, gamma globulin cannot be administered to the personal associates of persons with the disease in sufficient time to prevent the disease. Community-wide use of this material has not been shown to produce substantial benefits.[3] Gamma globulin is therefore of little practical value in the mass control of poliomyelitis. It does, however, have value in individual instances when given before exposure to virus.

SALK VACCINE

Salk succeeded in developing a vaccine in which there is virus inactivation by chemical means. The Salk vaccine is an aqueous suspension of inactivated poliomyelitis virus prepared from a selected strain of each of the three virus types grown on monkey kidney cells. The formaldehyde inactivation is designed to render the virus harmless, while preserving its capacity to induce production of antibodies.

To be suitable for widespread application, a preventive agent should meet the following criteria: 1. It must be safe; that is, there must be assurance that it will not produce or provoke disease and that untoward or undesirable reactions will be negligible. 2. It must be effective. It must either prevent the occurrence of the disease or modify its severity to an appreciable degree. 3. The method of administration must be practical of application in private and in public health practice. The available evidence indicates that the Salk vaccine meets each of these criteria. This evidence comes from studies conducted by Salk, from tests of pharmaceutical laboratories, and from a large-scale field trial carried out during the spring and summer of 1954 under the sponsorship of the National Foundation for Infantile Paralysis. The field trial was a controlled study in which about 450,000 children, 6 to 9 years of age, in 44 states, received the vaccine. An additional 200,000 children were injected with a placebo material, and 725,000 children represented uninjected, observed controls. Thomas Francis Jr., of the University of Michigan, who was in charge of the evaluation, presented a comprehensive analysis of the results on April 12, 1955.[4] The report indicated that the vaccine had been safe and effective in substantially reducing the risk of paralytic poliomyelitis

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1. Salk, J. E.: Studies in Human Subjects on Active Immunization Against Poliomyelitis: I. A Preliminary Report of Experiments in Progress, J. A. M. A. **151**: 1081 (March 28) 1953; Studies in Human Subjects on Active Immunization Against Poliomyelitis: II. A Practical Means for Inducing and Maintaining Antibody Formation, Am. J. Public Health **44**: 994 (Aug.) 1954.

2. Howe, A.: Acute Poliomyelitis, in Rosenau Preventive Medicine and Hygiene, edited by K. F. Maxy, ed. 7., New York, Appleton-Century-Crofts, Inc., 1951, pp. 292-310. Collins, S. D.: The Incidence of Poliomyelitis and Its Crippling Effects, as Recorded in Family Surveys, Pub. Health Rep. **61**: 327 (March 8) 1946.

3. An Evaluation of the Efficacy of Gamma Globulin in the Prophylaxis of Paralytic Poliomyelitis as Used in the United States 1953, Public Health Monograph 20, U. S. Public Health Service Publication 358, Department of Health, Education, and Welfare, 1954.

4. Francis, Jr., T., and others: Evaluation of 1954 Field Trials of Poliomyelitis Vaccine: Summary Report, Am. J. Pub. Health **45**: 1 (May, pt. 2) 1955.

in the vaccinated groups. The gross calculated degree of protection ranged from 60 to 90%; 60 to 70% effectiveness was found against disease caused by type 1 virus, the most prevalent type in cases of paralysis, and 90% or more effectiveness against that caused by type 2 and type 3 virus.

After its effectiveness was demonstrated in the field trial, the vaccine was licensed on April 12 for general use this year. Under sponsorship of the National Foundation for Infantile Paralysis, a large-scale immunization program was begun the second week in April among first and second grade school children. On April 12, Salk described a dosage schedule,[5] based upon antibody response studies, of three injections of 1 cc. each, to be given intramuscularly. The first and second injections are separated by an interval of two to six weeks and the third follows in approximately seven months. This differs from the schedule used in the field trial, when all three injections were given within a period of five to six weeks, only in the spacing of injections. Salk has presented evidence that the second injection is beneficial even if given after a number of months, and that giving the third injection about seven months after the first should induce a better antibody response than giving it earlier. In general, the revised schedule described by Salk was adopted for use in the vaccination program for first and second grade children sponsored by the National Foundation for Infantile Paralysis. The inadequate supply of vaccine has led to delay, in most instances, in giving the second injection.

DISTRIBUTION METHODS

The short supply of vaccine led to consideration in May of distribution methods and the establishment of age group priorities.[6] Under a voluntary plan of allocation and distribution, with age priorities based on risk of attack, the vaccine will be made available first to the children at greatest risk. For the country as a whole, the highest attack rates occur among children 5 to 9 years of age. The National Advisory Committee on Poliomyelitis Vaccine, which was established by the Secretary of the Department of Health, Education, and Welfare to study this problem, therefore recommended that this age group receive first priority. The committee has further recommended that, as vaccine becomes available, the existing priority group be broadened by adding, in equal proportions, children below 5 and above 9 years of age.

5. Salk, J. E.: Vaccination Against Paralytic Poliomyelitis: Performance and Prospects, Am. J. Pub. Health **45**: 575 (May) 1955.

6. Report to the President by the Secretary of Health, Education, and Welfare on Distribution of the Salk Vaccine, May 16, 1955.

7. Hill, A. B., and Knowelden, J.: Inoculation and Poliomyelitis: A Statistical Investigation in England and Wales, in 1949, Brit. M. J. **2**: 1 (July 1) 1950. Korns, R. F.; Albrecht, R. M., and Locke, F. B.: The Association of Parenteral Injections with Poliomyelitis, Am. J. Pub. Health **42**: 153 (Feb.) 1952. Rosen, L., and Thooris, G. C.: Poliomyelitis in French Oceania: Epidemiologic Observation on an Outbreak with Notes on the Incidence of Paralysis Following Intramuscular Injections, Am. J. Hyg. **57**: 237 (March) 1953.

8. Recommendation on the Use of Poliomyelitis Vaccine During the Summer of 1955, New York, National Foundation for Infantile Paralysis, 1955.

9. Hammon, W. M.; Coriell, L. L., and Stokes, J., Jr.: Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis: Plan of Controlled Field Tests and Results of 1951 Pilot Study in Utah, J. A. M. A. **150**: 739 (Oct. 25) 1952.

10. Bodian, D.: Neutralization of Three Immunological Types of Poliomyelitis Virus by Human Gamma Globulin, Proc. Soc. Exper. Biol. & Med. **72**: 259 (Oct.) 1949.

Medical organizations have agreed to follow a voluntary control plan under which physicians will vaccinate persons only within the priority groups. This places responsibility on the individual physician, with respect both to the use of the vaccine and to the education of his patients to accept use only in the priority age groups.

PROVOCATION

The possibility that the phenomenon of provocation might be involved in the injection of vaccine during periods of high incidence or epidemics has aroused considerable discussion among physicians and scientists.[7] On June 18, the National Foundation for Infantile Paralysis convened its Vaccine Advisory Committee, representatives of certain professional groups, and special consultants, to consider this problem. The organizations represented included the American Academy of Pediatrics, the Academy of General Practice, the American Medical Association, the American Public Health Association, the Association of State and Territorial Health Officers, and the U. S. Public Health Service. The group agreed unanimously [8] that "the total preventive effect of the vaccine in a period of rising poliomyelitis incidence should be much greater than the possible hazard from the provoking effect of the injection. Those present also concluded that the benefit to be gained by poliomyelitis immunization, in contrast to the small potential risk of provocation, increases in proportion to the severity of the poliomyelitis incidence, since a larger number of paralytic cases should be prevented during the entire period of the epidemic."

This general recommendation was based on information available at this time. Specifically, the vaccine is expected to produce some antibody within a week to 10 days after the first injection, and even small amounts of antibody may have some effect in preventing paralytic poliomyelitis. Therefore, "the onset of antibody response to the vaccine may eliminate any subsequent provoking effect of the vaccine injections." The evidence for this includes experience with the use of gamma globulin during a 1952 epidemic in Sioux City, Iowa,[9] experiments on development of immunity in monkeys,[10] and observations on the occurrence of poliomyelitis in the southern states during the 1954 vaccine field trial.

Contraindications to the use of vaccine during periods of high incidence cited by the group [8] were: (1) symptoms of minor illness, especially fever, sore throat, or gastrointestinal upset at the time of the proposed injection; and (2) occurrence of a case of poliomyelitis in the household immediately preceding the proposed injection. It is known that almost all the other members of the household are already infected when paralysis first appears, so that vaccine cannot be expected to protect against an already existing infection, and an injection at that time might provoke paralysis in the course of an otherwise inapparent infection.

SAFETY OF VACCINE

The question of safety of the Salk vaccine has also been the subject of considerable public and professional discussion. During the vaccine's development, field trial, and initial use, many problems arose, which were dealt with through close cooperation between Salk, the manu-

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facturers, and the Laboratory of Biologics Control of the Public Health Service. The experience that had been gained by April 12, 1955, established confidence in the safety of the experimentally produced vaccine and provided the basis for requirements designed to assure safety, purity, and potency.

The value of the vaccine as demonstrated in the 1954 field trial, plus the over-all experience and competence of the firms producing the vaccine and the participation of the Laboratory of Biologics Control in the field trial testing and subsequent developments, led to prompt licensing of the six pharmaceutical manufacturers whose applications were pending. Most of the lots of poliomyelitis vaccine were released on review of protocols, i. e., the manufacturer's detailed reports on manufacture and testing of each lot.

The occurrence of poliomyelitis among children receiving vaccine from the Cutter Laboratories led the Public Health Service to request this manufacturer to withdraw its product, and the company complied immediately. A thorough investigation of the plant and its manufacturing processes was instituted. Extensive laboratory tests of the material and field observations of the occurrence of all poliomyelitis cases were begun. Shortly thereafter, the in-plant study was extended to other members of the industry in order to determine whether there were common problems relating to production methods and to the adequacy of the testing requirements. This led to a temporary suspension of the nationwide vaccination program.

The investigation indicated that the records that the manufacturers had been required to submit did not bring out certain important data on processing and testing. Manufacturing experience revealed that inactivation of virus in the production of vaccine did not always follow the predicted course, inasmuch as infective virus was sometimes detected after the expected completion of inactivation. This meant that greater dependence must be placed as an integral part of process control, on tissue culture testing of larger volumes of vaccine to detect small quantities of residual live virus.

Changes incorporating this new knowledge were made in processing control and safety testing. New principles of testing were added to the Minimum Requirements for the production of poliomyelitis vaccine.[11] These principles should result in a product essentially free of live virus. On the basis of probability computations, a liter of the vaccine made under the amended requirements should contain 5 or more live virus particulates less than once in 100,000 times (see this issue, page 1249). Risk of transmission of poliomyelitis through use of such vaccine is negligible. Remember, however, that 100% safety cannot be assured for the poliomyelitis vaccine, just as it cannot be assured for other biologicals used in preventive and therapeutic medicine.

NEED FOR CONTINUING STUDY

It has been obvious from the time of the field trial that the vaccine needs further study and observation. Precise knowledge of the vaccine is limited to the experience and data gained as a result of that trial. The effectiveness of the vaccine has not yet been studied in age groups other than those observed in 1954. Research and additional experience with application of the vaccine should enable us to fill many gaps in our knowledge. It must be remembered that the need for continuing study of poliomyelitis in general and of this vaccine in particular is no different than the need for continuing study of other diseases and of the preventive and therapeutic agents.

The field trial provided no data on the effectiveness of the vaccine in children under 6 or over 9 years of age. The data indicated, in fact, that the greatest amount of protection occurred among children 9 years of age and that the degree of protection decreased progressively with age. Although Salk has presented data showing that children under 6 developed antibodies after injection, the relationship between antibody development and protection against paralytic poliomyelitis in these younger children is still under study. There is, therefore, need for additional information and for careful evaluation of the vaccine's effectiveness in both older and younger children. The answers can come only if large numbers of children are vaccinated and observed.

Optimum dose and interval between injections represent other problems needing additional study. Here again firm knowledge is limited to the field trial experience. The effectiveness of the vaccine under the modified dosage schedules that have been recommended for use this year remains to be determined. The question of duration of protection and the best timing of "booster" shots cannot be answered at this time. It is not yet known whether additional injections will be needed at stated and frequent intervals or whether the first series will provide protection for an extended period of time. Salk has observed detectable levels of antibody for 28 to 30 months after vaccination (see this issue, page 1239).

Additional research is also going forward on safety of the vaccine. The Mahoney virus strain, a strain of type 1 virus that is highly antigenic but is also highly invasive, is now employed in the vaccine. In order to provide an additional margin of safety, there is general agreement that a type 1 strain that has satisfactory antigenic properties but that is less invasive should be sought, with a view to substituting it in the vaccine. Several laboratories are now working on this problem. Other problems related to virus vaccines and the control of poliomyelitis will be under study. Among these are the combination of the Salk vaccine with other prophylactic agents, just as diphtheria and tetanus toxoids are now administered together, and the development of vaccines based on different principles than those employed in the Salk process.

Although we can expect further research and observation to lead to improvements, the vaccine is, at present, our most useful weapon in the prevention of paralytic poliomyelitis. Its development has opened the way for new achievements in poliomyelitis control. This medical discovery, like others in the past, brings new opportunities in preventive medicine to the practicing physician and the public health worker.

11. Technical Report on Salk Poliomyelitis Vaccine, Public Health Service, Department of Health, Education and Welfare, June, 1955.

DISCUSSION OF PANEL ON PROSPECTS FOR CONTROL OF POLIOMYELITIS

DR. ALBERT SABIN, Cincinnati: With full appreciation for the important recent advances in our knowledge of immunization against poliomyelitis, it may nevertheless be said that the prospects for the control of poliomyelitis depend more on what still remains to be learned than on what has been learned thus far. Salk has demonstrated that a sufficiently potent, formalinized vaccine can be prepared in the laboratory to produce antibody in children who had none to begin with, and the extensive field trial of 1954 has provided evidence that the incidence of paralytic poliomyelitis in school children can be significantly reduced even by vaccines that are not of optimal potency. The important questions now before us are concerned with the quantitative aspects of the safety and effectiveness of such vaccines produced on a mass scale for mass use in human beings of all ages. The most recent experience has shown that it is possible to prepare many large lots of formalinized vaccine that can be administered to millions of children with impunity. On the other hand, the circumstances surrounding the serious epidemic of type 1 paralytic poliomyelitis that has followed the use of two large lots of mass-produced vaccine indicate that the originally prescribed safety tests do not with regularity detect minimal amounts of virus that can become a source of considerable danger. This is due to the fact that at least one of the components of the vaccine, the type 1 virus, is the most virulent strain studied thus far. More recently material produced by another company has come under suspicion because of the occurrence of a small but disproportionately unexpected number of paralytic cases, in some of which there was initial paralysis in the inoculated extremity. It is possible that the more stringent safety tests that were recently recommended by the U. S. Public Health Service may avoid such accidents in the future, but the effectiveness of these new procedures has not yet been established by tests on the lots of vaccine that have proved dangerous in recent weeks. Children without antibody may be as susceptible to minute amounts of fully virulent virus as any tissue culture bottle or monkey. Therefore, 100,000 children may still be better indicators of minute amounts of virus that have not been inactivated than the smaller numbers of tissue culture bottles and monkeys that can be used practically in the most rigid safety tests. Accordingly, it would seem to me highly desirable to replace the virulent viruses currently used in the preparation of formalinized vaccine by experimentally segregated or naturally occurring antigenically potent strains that are dominantly avirulent for monkeys by both the intracerebral and the intramuscular routes. While a single tissue culture dose of the virulent type 1, Mahoney virus can produce paralysis in intramuscularly inoculated monkeys, 10 million tissue culture doses of the avirulent variants can be inoculated without producing paralysis. We now have such strains for each of the three types, and their antigenic potency after formalinization is now being investigated in Sweden and in England by the quantitative method of assay in guinea pigs developed by Dr. Sven Gard and his associates.

The antigenic potency of mass-produced formalinized vaccines must be carefully controlled by an adequate, quantitative method of assay if the expected protection is to result from their use. Salk's standard reference vaccine even in one dose seems to produce antibody more regularly than the three doses of most vaccines used in the 1954 field trial. Whether the various factors responsible for deterioration of antigenic potency in the 1954 vaccines have now been overcome and whether the current trend for more prolonged "cooking" with formaldehyde solution (Formalin) in an attempt to achieve a greater margin of safety might affect antigenic potency—these are both questions that cannot now be answered, because the estimates of potency currently in use in this country either are not sufficiently quantitative or are unrelated to human response. Studies recently completed and communicated to me by Dr. Sven Gard in Sweden indicate that the guinea pig method of assay yields quantitative data similar to those obtained in children without antibody and should therefore become a useful tool for safeguarding the potency of formalinized poliomyelitis vaccines. If one can be assured of getting mass-produced vaccines as good or nearly as good as Salk's standard reference vaccine, one might look forward to better results than were obtained in the 1954 field trial, when the effect decreased progressively in younger age groups to a point where the protection afforded 6-year-old children was not regarded as statistically significant.

And how long will the protective effect of the best formalinized vaccine last? The only honest answer, of course, is that we do not know. If not more than the currently proposed three doses are given, time will provide some sort of answer only if the poliomyelitis surveillance unit established by the Public Health Service during the recent emergency will continue its excellent work for as long as it may be necessary to obtain an answer. Salk's hypothesis that natural infection may itself provide the booster for an accelerated antibody response and thus prevent paralysis is based on observations following intramuscular injections of preformed antigen but is not supported by any data on the effect of feeding virus. My own observations on feeding attenuated viruses to volunteers with barely detectable or minimal amounts of antibody indicate that the antibody response in such people is usually not accelerated.

Will widespread immunization of the younger age groups with formalinized vaccine interrupt the chain of infection and thus eliminate the paralytic disease that in many countries with advanced standards of hygiene is now such a serious problem in those persons who are over 20 years of age? Again the honest answer is that we do not know, for alimentary infection in the presence of antibody may depend on the size of the infective dose, and this also must be investigated in greater detail in the future. A recent serologic survey completed in my laboratory indicated that among eighty-three 21 to 30-year-old Americans of the middle income groups 57% had no

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demonstrable antibody for type 1 and 87% lacked antibody for one or another type of poliomyelitis virus. These people also need protection against paralytic poliomyelitis, and if a vaccine provides only transitory immunity we may well raise a highly susceptible adult population that would be in great danger if a highly virulent poliomyelitis virus were suddenly introduced in their midst from the outside world.

Should we wait for years to find out what the best killed virus vaccine will do, or should we now increase our efforts to learn everything we can about the possibility of imitating the mechanisms by which natural infection imparts lifelong immunity? I think it would be poor strategy to wait. The experiments carried out in my laboratory on experimentally segregated and naturally occurring attenuated poliomyelitis viruses of all three types, the recovery by Li and Schaeffer of an especially avirulent type 1 strain derived from the Mahoney virus, and the experiments of Koprowski and his associates with attenuated types 1 and 2 viruses all indicate that suitable strains are now available for pursuing this problem slowly and cautiously but nevertheless vigorously.

My own studies on human volunteers have already indicated that the ingestion of as little as 0.001 cc. of culture fluid of any of the three types or simple swabbing of the throat with minute amounts of virus can induce symptomless immunogenic infections. It is especially noteworthy that the attenuated viruses possess the significant characteristic of not producing viremia despite extensive multiplication somewhere in the alimentary tract. Neither the original attenuated viruses nor the progeny resulting from multiplication in the alimentary tract produce paralysis in chimpanzees after direct inoculation of large doses into the gray matter of the spinal cord.

It would be fine if it should turn out that there were no need for the practical application of the information acquired from careful studies on attenuated viruses, but it would be a pity not to have this knowledge in reserve if it should turn out that it were needed for the ultimate control of poliomyelitis on a world-wide basis. Let us not confuse the first great victory with total victory, and let us not disband too soon the great poliomyelitis army and general staff that has made the present advances possible. Finally, let us be guided by the words of Sir Francis Drake, who said: "Grant us to know that it is not the beginning, but the continuing of the same until it is thoroughly finished, which yieldeth the true glory."

DR. JOSEPH STOKES JR., Philadelphia: In discussion of poliomyelitis vaccination at this critical period following Dr. Francis' and Dr. Salk's most valuable reports of success in children with certain batches of vaccine; and following the later reports of infective batches of vaccine in the United States resulting in a crippled vaccination program; and finally when the season for the disease is upon us, it would not appear worthwhile in this panel to review the difficult problems of public relations. The primary question on every physician's mind here today, in fact in the entire country both among the medical profession and the lay public, is with respect to the safety of the vaccine and not with respect to its potency.

I had no opportunity to see these papers, except a considerable portion of Dr. Salk's, before this morning but have been impressed again with how easy it is to discuss increases in antibodies and how difficult it is to come to grips with the question of safety. It has been tempting when drawing a curve of inactivation of virus by formaldehyde solution (Formalin) to make it a straight line, showing complete inactivation of the virus within a few days. We have seen such a straight line this morning. To my knowledge laboratories working in this field, and I have talked to a considerable number in the last few days, all have agreed that the inactivation of the poliomyelitis viruses by formaldehyde solution, 1:4,000, in a majority of instances is not a straight line but a curve that varies at times up to the point of being almost asymptotic.

Since testing samples of vaccine for infective virus must be random at present, and if the curve of inactivation by formaldehyde solution, in a majority of instances, is not a straight line, then the infective particles may be missed in such sampling procedures. In this respect it would be extremely helpful if methods of concentration and purification of the virus were available for such testing for infective particles so that the sampling would afford more complete information. Such methods are now being made available. But at present there is no way of being completely certain that batches of vaccine are not infective. If the inactivation of virus is a curve in the majority of instances, then there may be a very narrow separation between a vaccine batch that is infective and a batch that no longer has potency for immunizing. It has been said that the infective batch or batches mentioned this morning were carefully reviewed with respect to their method of preparation and that no essential difference was found, except the method of preservation, between the preparation of these infective batches and other batches of vaccine. I believe this to an extent is the crux of the fear expressed concerning safety, in that no specific fault has been demonstrated that has separated the infective batches from others until Dr. Shannon's report this morning. It is fortunate that in Canada, where 700,000 doses of vaccine have been administered without evidence of infection, one laboratory has been responsible for the production of all of the vaccine, but, when the range between infectivity and potency may be very narrow, the necessary multiplication of laboratories for production would seem to enhance the dangers.

Also, I should appreciate some discussion from Dr. Salk of the possibility of reactivation of virus after standing when the formaldehyde has been neutralized, or of reactivation after injection. I am glad to hear him say that he feels the less virulent and yet antigenically active strains of type 1 should be used in preference to the highly virulent, but not so antigenically active, Mahoney strain used in the original trials.

It is important to remember that the reports we have heard are but one step, although a very important one,

in the long road ahead toward the control of poliomyelitis. In considering this slow progress in such control I should like to ask three fairly simple questions: 1. Why not protect the central nervous system with passively transferred antibodies either administered parenterally or acquired transplacentally while the individual is exposed by the natural alimentary route to attenuated living virus that does not produce paralysis in monkey or man? 2. Would this procedure not involve a lesser risk than a possible escape of a few particles of living, but fully virulent, virus from formaldehyde-inactivated vaccine, which at times may not be inactivated, and which is administered by the unnatural parenteral route to the most susceptible species, man? 3. Why run the risk of precipitating paralysis of a limb by injection of any material other than antibodies in an individual who may be harboring virulent virus?

Five years ago, Koprowski, Jervis, and Norton, who originated the use of attenuated living virus, fed a group of young children live, attenuated type 2 poliomyelitis virus (the T N strain) in the form of cotton rat cord tissue. None of the children showed signs of illness or any untoward reaction following the oral administration of virus, and all developed homotypic antibodies in their blood. Subsequently, Koprowski, Jervis, and Norton demonstrated that the level of protective antibodies remained high during a four year observation period after the single feeding of modified live virus. In the course of the past three years, a type 1 strain of virus (the S M strain) became attenuated and proved to be nonpathogenic for laboratory primates when injected intracerebrally. This strain was then employed by these investigators for oral administration to a group of 15 children who had no poliomyelitis antibodies prior to feeding. The results were most encouraging, since all of the children who ingested virus developed homotypic antibodies, again without the slightest sign of illness.

In the course of these and more recent clinical trials conducted by Koprowski, Jervis, Norton, and myself, observations were made on the response of nonimmune individuals to the simultaneous feeding of types 1 and 2, as represented by the SM and TN strains respectively. Good antibody responses were obtained in 22 children who received gamma globulin immediately after being fed the SM strain of type 1 virus, thus indicating that the gamma globulin did not seem to affect the antigenic activity of the attenuated virus. Each of the 22 individuals developed antibodies with no sign of illness after becoming an intestinal virus carrier. Similar results have been obtained with the T N strain of type 2 virus.

I have mentioned these results to indicate a possible method of immunization that could presumably require no parenteral injections in infants and perhaps a single injection of gamma globulin in older children, while at the same time permitting the development of active immunization during the period of passive immunity afforded to infants by the mother, or in older children by the gamma globulin. Such a method is obviously in its earliest experimental trials, but the results already obtained fully warrant further active study.

QUESTIONS AND ANSWERS

The following questions were among those asked by the members of the audience at the Panel Discussion on Poliomyelitis held as part of the Annual Meeting of the American Medical Association, Atlantic City, June 7, 1955. The answers to these questions were given and subsequently edited by the members of the panel under the direction of the moderator, Dr. Van Riper; the questions have been grouped together under various headings.—ED.

Vaccine Preparation and Storage

QUESTION: How long does it take to prepare each lot of vaccine if it passes each test satisfactorily? What is the shortest number of days?

ANSWER: A total of 120 days is required to complete the processing from virus culture to final testing of the packaged vaccine.

QUESTION: What antigenicity tests are done on the various lots of various producers to assure uniform lots of vaccine?

ANSWER: The antigenicity tests done on the various lots of vaccine to assure uniformity are made by vaccinating groups of 12 monkeys and testing the serum antibody level against each of three types after a standard schedule of immunization. For this purpose three doses a week apart are administered and blood drawn one week after the third dose. The level of antibody induced by the unknown vaccine is compared with that induced by a standard preparation referred to as reference vaccine "A." The geometric mean level of antibody induced by the test vaccine must be equal to or greater than a certain level as compared with reference vaccine "A." A vaccine that fails to pass such tests for all three types is considered unsatisfactory for use.—JONAS E. SALK, M.D.

QUESTION: For inactivation are these the total processes used: Formalin, heat, dilution, and usual sterile processes of manufacture?

ANSWER: The virus fluid is filtered, formaldehyde solution (Formalin) is added to it in concentration of 1:4,000 and it is then incubated at 37 C until all virus particles have been inactivated.

QUESTION: Do the present vaccines lose their potency with age? Do you recommend refrigeration storage of the vaccine?

ANSWER: The vaccine, under present standards, has a six month expiration date. It should be stored under refrigeration at a temperature between 35 and 50 F, the lower limit being preferred. Freezing should be avoided.

QUESTION: Could you relate the names Brunhilde, Lansing, and Leon to virus type (either 1, 2, or 3) and to the names Mahoney, MEF, and Saukett now being used?

ANSWER: Brunhilde and Mahoney are strains of type 1, Lansing and MEF-1 strains of type 2, and Leon and Saukett strains of type 3 virus.

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Safety Tests

QUESTION: What safety tests are now used: bacteriological, monkey inoculation, other animals, tissue culture? Are these tests done on all lots?

ANSWER: Prior to inactivation each virus pool is tested for the presence of B virus and Mycobacterium tuberculosis. After inactivation each monovalent strain pool is tested for infectious virus by tissue culture methods. Each lot of trivalent vaccine is tested for infectious virus by tissue culture methods. The final vaccine pool is tested for lymphocytic choriomeningitis virus in mice inoculated intracerebrally. The final vaccine pool is tested for residual active poliomyelitis virus by intracerebral inoculations into 12 rhesus or cynomolgus monkeys and intramuscular inoculations into 6 cynomolgus monkeys.

QUESTION: Is it clear that after the new safety measures outlined by Dr. Shannon the vaccine will still be as potent as the vaccines used in the field trial?

ANSWER: The added safety testing does not in any manner affect the potency of the vaccine.

QUESTION: Does vaccine now in hands of state and school health departments meet new safety standards for resumption of inoculation programs? So far as we know these lots have not been recalled and retested.

ANSWER: All lots of vaccine in the hands of public health departments meet the revised standards for production and testing. All lots not meeting these requirements have been recalled by the manufacturer.

QUESTION: 1. Was each lot of vaccine used in 1954 approved by the manufacturer, by Dr. Salk's laboratory, and by the National Institutes of Health before release? 2. Was the same procedure followed for all vaccine in 1955? If not, please give details.

ANSWER: 1. Yes. 2. The licensed vaccine released by the surgeon general of the U. S. Public Health Service for use in 1955 was tested for safety, potency, and sterility by the manufacturer. In some instances complete or total testing for safety, potency, and sterility was carried out by the National Institutes of Health.

QUESTION: Are the controls of vaccine made at Connaught Laboratory in Canada similar to the United States controls? The program was continued in Canada.

ANSWER: The vaccine produced by the Connaught Laboratories in Toronto, Canada, for use by the Canadian Provincial Health Departments, was made in the same way in which the vaccine was produced in the United States. The Connaught Laboratories tested the vaccine for safety, potency, and sterility and concurrently the product was tested by the Dominion Laboratories in Ottawa. The program was continued in Canada with approximately one million children receiving two doses of vaccine, without the development of a single case of associated paralysis.

QUESTION: Were tissue culture tests (in various concentrations) used in 1954 vaccine?

ANSWER: In 1954 the vaccine was tested for presence of viable virus both in tissue cultures and by monkey inoculation.

Vaccine Dosage and Schedule of Administration

QUESTION: What is now considered to be the ideal interval between the three injections?

ANSWER: The present recommended schedule for vaccine administration is: (1) 1 cc. of vaccine injected intramuscularly; (2) 1 cc. of vaccine injected intramuscularly two to four weeks following the first injection; and (3) a booster shot of 1 cc. injected intramuscularly not sooner than seven months after the second dose and prior to the onset of the next epidemic season.

QUESTION: How long after the first injection can the second one be given and still produce what would be considered an effective immunization?

ANSWER: It has been reported that the sensitization of the individual that results from the first injection of vaccine is not lost if the second dose is delayed for as long as six months to a year; however, optimal protection cannot be anticipated until the complete series of three injections has been given. Dr. Salk has indicated that total antibody response is in direct proportion to the total mass of the antigen.

QUESTION: Is it advisable to administer the second dose of poliomyelitis vaccine as late as two months after the first dose? Our first injections were given April 25, 26, 27, 1955 in Memphis, Tenn. Vacation period began June 3, 1955.

ANSWER: The second dose of vaccine should be given as soon as the vaccine is available provided a period of at least two weeks has elapsed since the first injection.

QUESTION: First doses of vaccine were given many weeks ago. A long delay has ensued. Shall we now ignore the first dose and begin with a new first dose?

ANSWER: The effect of the first dose of vaccine is not lost if the second dose follows the first within a 12 month period.

QUESTION: How would 2 cc. of vaccine given affect (1) immunity response and (2) undesirable reactions?

ANSWER: 1. The use of 2 cc. of vaccine as the primary sensitizing mass would probably not be any more effective than 1 cc. 2. Many instances are reported of children having received 2 cc. of the vaccine without reaction.

QUESTION: Because of three types of virus, it is advisable to vaccinate previously infected children and adults?

ANSWER: Yes. Paralytic consequences of poliomyelitis infection give immunity only to the virus of the type that caused the paralytic infection. The individual remains susceptible to paralytic infection by the other two types until complete immunity is attained to all three types.

QUESTION: In light of the fact that the Salk vaccine is a pooled three-virus vaccine, what would you advise concerning vaccination in the case of 9-year-old child who last summer had poliomyelitis affecting the right side of the body? Should one give the pooled vaccine or only use the two viruses in separate vaccination to immunize against bulbar involvement?

ANSWER: All three types of virus may produce the same paralytic consequences. Until a simple, readily available test for immunity is developed, an individual who has already suffered a paralytic attack of poliomyelitis should receive the trivalent vaccine.

Clinical Questions

QUESTION: Does the poliomyelitis vaccine protect against the whole disease (such as enteric manifestations) or does it simply prevent the paralytic form?

ANSWER: The vaccine does not protect the individual from subsequent enteric infection; where effective the vaccine only protects aginst the paralytic consequences of systemic infection.

QUESTION: Does the Salk vaccine have any use in treatment of poliomyelitis?

ANSWER: No.

QUESTION: If poliomyelitis does develop in spite of injection with the Salk vaccine, is the clinical picture and symptom pattern the same as the usual picture of poliomyelitis or is there any alteration or modification of symptoms?

ANSWER: An individual incompletely immunized may present clinical symptoms similar to those seen in a vaccinated person. The Francis report suggested that, where clinical infection occurred in spite of vaccination, it was less severe.

QUESTION: Should we postpone tonsillectomies until the end of the poliomyelitis season because of the danger of precipitating bulbar poliomyelitis in children or in close contacts of children who have been inoculated with Salk vaccine produced under the old standards for safety in which there is no certainty that all the virus in the vaccine is actually killed?

ANSWER: Elective tonsillectomies should be postponed when cases of poliomyelitis are being reported in the community. This practice should be continued until there is further evidence as to the effectiveness of the immunization that results from the use of the Salk vaccine.

Contraindications

QUESTION: Please list specific contraindications to poliomyelitis immunization. What of immunization to children recently ill with repeated upper respiratory infections?

ANSWER: The same contraindications to use of poliomyelitis vaccine should be observed as in the use of other comparable biologicals. Vaccination should be delayed where an individual has had known contact with a paralytic poliomyelitis infection, either in the home or among close intimate contacts. A child who evidences illness should not receive the poliomyelitis vaccine.

QUESTION: Are there any contraindications to giving the poliomyelitis vaccine shortly after recovery from illnesses such as chicken pox, mumps, purulent meningitis, or acute encephalitis?

ANSWER: As soon as an individual is completely recovered from an infection such as chicken pox, mumps, purulent meningitis, or acute encephalitis, it should be perfectly safe to carry out a course of poliomyelitis vaccination.

QUESTION: Is there any contraindication to the giving of other vaccines (typhoid, tetanus toxoid) at the time of giving poliomyelitis vaccine?

ANSWER: There is no reason to believe that a multiple antigen may not be given, and eventually poliomyelitis vaccine may be given combined with other biologicals.

Reactions to Vaccine

QUESTION: What are the percentages, approximately, of reactions to the first inoculation of vaccine in school children in 1955?

ANSWER: Untoward reactions following the administration of properly inactivated poliomyelitis vaccine have been minimal. This matter was thoroughly explored and presented in the Francis report evaluating the 1954 field trial. No major reactions could be attributed to the vaccine. Minor reactions were as frequent among children who received placebo as among those who received vaccine; namely, 0.4%. Experience in the 1955 vaccination program has not been evaluated in the same way as data collected for the 1954 field trial evaluation; however, there is no reason to believe that the incidence of reactions to properly prepared vaccine was any higher in 1955 than in 1954.

QUESTION: Is there any possible danger of horse serum allergic reaction to the Salk vaccine?

ANSWER: There appears to be no danger of allergic reactions in persons sensitive to horse serum.

QUESTION: What authorities on Rh erythroblastosis have approved the safety of the poliomyelitis vaccine from the standpoint of Rh trouble? What are views of Levine and Wiener?

ANSWER: Wiener is on record as having stated that Rh-Hr sensitization would not result from the use of the Salk vaccine.

QUESTION: What are the possibilities of developing chronic glomerulonephritis with repeated use of the Salk vaccine?

ANSWER: Adequate follow-up on a number of individuals who have received repeated injections of the Salk vaccine fail to show the development of any evidence of kidney damage.

QUESTION: May allergy injections such as "cold vaccine" be given in close proximity (one week) to administration of poliomyelitis vaccine?

ANSWER: Yes.

Negative Phase

QUESTION: Has any investigative work been done or, if not, will investigative work be done in the immediate future to determine whether children who have titratable levels of poliomyelitis antibodies in their blood as a result of either prior poliomyelitis infection or inoculation of poliomyelitis vaccine will after receiving an injection of poliomyelitis vaccine experience a negative phase reaction, with marked drop in antibody titer during the first 24 or more hours after inoculation, before the antibody titer rises to new high levels? If such a negative phase does occur, the giving of poliomyelitis vaccine during poliomyelitis epidemic periods could pose a hazard to children who may already be immune and who harbor poliomyelitis virus in their intestinal tracts.

ANSWER: Studies have been done to determine whether or not a drop in antibody titer occurs after inoculation, and if there is any change it has not been perceptible even in individuals with low levels of antibody.—JONAS E. SALK, M.D.

QUESTION: Is there any increased susceptibility to poliomyelitis infection immediately after first vaccine dose? In other words, is there a negative phase?

ANSWER: This question can be answered in terms of antibody level wherein it is found that antibody level rises rather than declines after the first dose of vaccine. As for a single dose of vaccine increasing susceptibility, there are no theoretical reasons why this should be the case. In experimental animals it has been shown that antibody development and resistance to infection occur almost simultaneously.—JONAS E. SALK, M.D.

Epidemiological Questions

QUESTION: 1. What are the chances statistically that an immunized child will develop poliomyelitis from the vaccine? 2. What are the chances that an immunized child will develop poliomyelitis in spite of the vaccine? 3. What are the chances that a nonimmunized child will develop poliomyelitis?

ANSWER: 1. None from properly inactivated vaccine. 2. The chances that an immunized child will develop poliomyelitis in spite of having been vaccinated vary with the virus type. The chance of developing type 1 poliomyelitis is approximately 30% and of type 2 or type 3 perhaps 10%. 3. A study by Kumm on the risk of contracting poliomyelitis concluded that among children born in Connecticut, Massachusetts, New York, and North Carolina in 1930, 1931, or 1932, one out of every 156 acquired poliomyelitis in the first 20 years of life. Variations in this figure could be expected in different localities.

QUESTION: Dr. Francis referred to those who did not participate in the field trials as a "different population." What is meant by saying that the rate of poliomyelitis in this group is irrelevant and, if so, why? What is meant by "a different population?"

ANSWER: It has long been suggested that studies based upon volunteer participation possess an inherent difficulty if those who refuse to volunteer are accepted as controls. A number of studies have also pointed out that antibodies and resistance to poliomyelitis are acquired later in populations of high economic status than in the lower economic groups. There were indications that volunteering for participation in the evaluation program might well be influenced by such factors and consequently that those who refused would present characteristics that would suggest that they were really a more resistant segment of the population immunologically. A survey, to which reference has been made, did in fact yield results indicative that the "no's" were a different population. The population receiving vaccine and placebo are parts of the same population that requested participation, apparently similar in every way. The difference in incidence between placebo and uninoculated groups was thus anticipated. The uninoculated who refused inoculation are not part of the study.—THOMAS FRANCIS JR., M.D.

QUESTION: 1. Just what is meant by the vaccine being 60 to 90% effective? 2. Does it mean that in certain groups given the vaccine only 60 out of 100 showed protective antibodies?

ANSWER: 1. The effectiveness of the vaccine was measured by comparing the paralytic attack rate among those vaccinated with the rate observed among controls. Thus, if there are 60% less cases in the vaccinated than would be expected among the same children had they not been vaccinated, the vaccine is considered 60% effective. 2. No. Effectiveness was measured in terms of protection against paralytic disease, not by measuring presence or absence of antibodies.

QUESTION: 1. What is the hazard of giving vaccine in an epidemic season? 2. What is the hazard of giving a second dose?

ANSWER: 1. The hazard of giving vaccine in the epidemic season is less than the protection afforded by the vaccine. 2. Since the first dose of vaccine has already produced detectable antibody, though not enough to assure total protection, it is sufficient to eliminate any hazard in connection with the giving of the second dose of vaccine.

QUESTION: Instead of giving day-to-day reports on poliomyelitis vaccination or predicting by weeks and months, why not postpone start of immunization until fall months when possible poliomyelitis virus carriers will have diminished and possibility of activating a dormant virus will be less risky?

ANSWER: As soon as the supply of poliomyelitis vaccine is adequate to meet the demand, immunization will undoubtedly be carried out during the season of the year when poliomyelitis outbreaks are less likely to occur in each community.

Provoking Effect

QUESTION: What is the danger of giving intramuscular injections of poliomyelitis vaccine during the summer to children who might be contact carriers of poliomyelitis?

ANSWER: At a meeting held in New York City on June 18, 1955, it was concluded that "provocation" was minimal in connection with intramuscular injection of poliomyelitis vaccine; that the probable protection from paralytic poliomyelitis as opposed to the provocation of paralysis was so much greater that continued use of vaccine was recommended during the epidemic season.

QUESTION: Does the stick of the needle predispose to paralytic poliomyelitis if the patient has poliomyelitis virus in the gastrointestinal tract?

ANSWER: In the absence of viremia there is no evidence to support the belief that the mere puncturing of the skin would provoke an attack of paralytic poliomyelitis.

QUESTION: What about any injection during the poliomyelitis season? Even a blood cell count?

ANSWER: In the presence of viremia any parenteral injection may result in the localization of paralysis in the extremity into which the injection is made. This is especially true where the precipitated biologicals are used, such as tetanus toxoid, diphtheria toxoid, or pertussis vaccine. There is no evidence to support the belief that the mere puncturing of the skin or taking a blood sample for a blood cell count would precipitate an attack of paralytic poliomyelitis.

QUESTION: Is it safe to give poliomyelitis vaccine in the presence of an epidemic?

ANSWER: Yes—provided the individual has had no known contact with a paralytic case.

QUESTION: How late in the summer should immunization be begun?

ANSWER: It is recommended that primary immunization be given at any time in the year, recognizing that if the individual is already harboring the virus of poliomyelitis the vaccine will not protect against the paralytic consequences of that infection. Primary vaccination should not be given to an individual who has had recent contact with a case of poliomyelitis.

QUESTION: In a passive carrier of poliomyelitis virus does injection of vaccine predispose to infection?

ANSWER: In the presence of inapparent poliomyelitis infection there may be a slight provoking factor in connection with the use of the Salk vaccine. Since it requires 7 to 10 days for the vaccine to produce antibody, the vaccine cannot be expected to protect the individual from paralytic infection any more than the use of gamma globulin (giving passive immunity) can protect an individual already infected.

Virus Carriers

QUESTION: If there is the possibility of there being infective vaccine, might not children who received the vaccine and who do not become afflicted with poliomyelitis be carriers of the poliomyelitis virus?

ANSWER: Contact with live poliomyelitis virus, either under natural circumstances or that which may occur by injection of unsatisfactory vaccine in this respect, produces equivalent effects in terms of virus carriage. However, from large-scale field experience, it appears that family contact and other associated cases have been observed only in connection with the administration of lots of vaccine that have contained readily demonstrable quantities of infective virus. Lots of vaccine that are not harmful to the recipient have by the same token not produced recognizable secondary cases.—JONAS E. SALK, M.D.

QUESTION: Is there any danger of close association of uninoculated children with children who were recently inoculated with the Salk vaccine for the first or second time?

ANSWER: There is no danger of association between uninoculated and vaccinated children. As far as is known a vaccinated child may still become infected, since the vaccine protects against paralysis. However, it is known that animals who are solidly resistant to paralytic infection may still be infected with the virus and excrete it in their feces.

QUESTION: Will not poliomyelitis vaccination subject parents to the disease, which will start epidemics in the child population that has not been vaccinated?

ANSWER: A properly inactivated vaccine will not subject the parents to the disease; neither can it start an epidemic in the unvaccinated child population.

Vaccine Research Problems

QUESTION: What are the areas where more research is now urgent in the vaccine and control program?

ANSWER: The following areas of research deserve and are receiving attention: (1) duration in years of immunity to the paralytic disease following vaccination; (2) search for less pathogenic but still highly antigenic strains of virus that might be substituted for those now in use; (3) search for stable strains of attenuated virus that could be used as live virus vaccines; (4) methods of concentrating the vaccine to render the safety test more precise; (5) search for a stable strain of normal human or primate cells, susceptible to poliomyelitis virus, which will grow continuously in cultures and which would eliminate the necessity of importing monkeys from India; and (6) search for better methods of virus inactivation.

QUESTION: I heard a research man state recently that ultraviolet may prove superior to Formalin in inactivating poliomyelitis. What is the basis for this? Is it pH?

ANSWER: Several investigators are experimenting with the use of ultraviolet irradiation as a method of inactivation of the poliomyelitis virus. This is a physical as opposed to chemical (Formalin) inactivation.

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QUESTION: In studies on bacteriophage inactivated by x-ray irradiation there is evidence that the virus may later become activated on standing exposed to ordinary light; inactive virus particles combining to form live virus. Is there any danger of an analogous recombination for inactivated poliomyelitis virus to produce infective virus, particularly in a trivalent vaccine?

ANSWER: In the first place the experiments spoken of were not done by x-ray irradiation but were done by the use of ultraviolet light. Bacteriophages inactivated in this manner were reactivated by exposure to ordinary light. This is not recombination. Bacteriophages inactivated by ultraviolet light and then allowed to adsorb on bacterial cells do, by multiplicity reactivation, produce a few live virus particles. Nothing of this kind has ever been accomplished with animal viruses. On the other hand, when an animal cell is infected by many live, properly marked influenza virus particles, evidence of recombination has been obtained. Finally, there is no reason to believe that poliomyelitis viruses, properly inactivated by formaldehyde solution (Formalin), will become active upon exposure to light, or through the mechanism of multiplicity reactivation, or through recombination.

QUESTION: For how long is there appreciable antibody titer in the blood after a single primary injection of 1 cc. of Salk vaccine?

ANSWER: It is not known for how long there is appreciable antibody in the blood after a single primary injection of 1 cc.

QUESTION: Why is not influenza virus vaccine as effective as poliomyelitis virus vaccine?

ANSWER: This question cannot be answered simply and assumes that influenza virus vaccine is not as effective as poliomyelitis vaccine, which may not be true.—JONAS E. SALK, M.D.

Gamma Globulin

QUESTION: 1. Does gamma globulin ("antipoliomyelitis") provide any safety against "virus introduction or stimulation" due to Salk vaccine? 2. If we assume that there is a slight possibility that live virus particles may escape the safety tests, why not give gamma globulin simultaneously in adequate doses (analogous to the old diphtheria toxin-antitoxin preparation)?

ANSWER: It is not recommended that gamma globulin be given prior to the use of the Salk vaccine.

QUESTION: In the absence of Salk vaccine, should we give prophylactic gamma globulin this summer?

ANSWER: In the event of an epidemic outbreak of poliomyelitis in a community gamma globulin is recommended for mass prophylaxis for the most susceptible age groups.

QUESTION: Why not protect with passive antibody (immune globulin) and infect with attenuated virus enterically?

ANSWER: Until such a time as safe attenuated live virus vaccine is available, it is impossible to consider passive immunization with gamma globulin to be followed by the administration of attenuated virus vaccine.

CLINICAL NOTES

ENDOCERVICAL FORCEPS FOR EVALUATION OF THE CERVICAL FACTOR IN INFERTILITY

Allan Palmer, M.D., San Francisco

A new instrument has been devised for the purpose of evaluating the cervical factor in the infertile female. The tenacity of the endocervical mucus often precludes obtaining a satisfactory specimen by suction with a pipette or other available instrument for the purpose of testing its flow elasticity (Spinnbarkeit), spermigration, and postcoital sperm activity. The endocervical forceps shown (figure) enables one to easily obtain an adequate specimen of mucus by simply inserting the closed instrument into the endocervical canal. When the instrument has been placed at the desired level between the internal and external cervical ora, it may be opened slightly, closed and locked, and then withdrawn. The lock on the instrument permits one to lay it aside momentarily without loss of the specimen, if there is to be a momentary lapse of time before it can be examined microscopically.

Endocervical forceps, with opposable tips (right).

The accurately fitting, smoothly concave opposable tips of the instrument (figure, right) enable one to detach and seal off a specimen of mucus regardless of its variable rheologic characteristics.

Flow elasticity (Spinnbarkeit) can be measured or evaluated by opening the instrument over a centimeter scale and measuring the length to which the specimen can be stretched before it breaks. The flow elasticity may be regarded as "excellent" if the tips of the instrument can be opened and the mucus stretched to 10 cm. without breaking. The same specimen can then be transferred to a glass slide for microscopic examination. A spermigration test can be made by putting a drop of seminal fluid alongside the mucus, or the mucus may be examined for postcoital sperm activity (Sims-Huhner test). The instrument can also be used, with sterile precautions, for obtaining specimens of cervical mucus for antibiotic sensitivity tests in instances of cervical "bloc." An instrument for the Sims-Huhner test that embodies the principal features of the endocervical forceps has been described by Kerner.[1]

2107 Van Ness Ave.

This instrument was exhibited at the 4th Annual Meeting of the Western Branch of the American Society for the Study of Sterility, Palm Springs, Calif., Nov. 12-14, 1954, and at the 104th Annual Meeting of the American Medical Association, Atlantic City, N. J., June 6-10, 1955.

1. Kerner, J. A.: An Instrument for the Sims-Huhner Test, Am. J. Obst. & Gynec. 66: 909, 1953.

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THE PRESENT STATUS OF POLIOMYELITIS VACCINE

Elsewhere in this issue of THE JOURNAL (page 1239) is a series of papers, discussion, and questions and answers by individuals interested in the use of the "Salk vaccine." At the A. M. A. meeting in Atlantic City in June of this year there was held a panel discussion on prospects for the control of poliomyelitis. The meeting was under the joint sponsorship of the A. M. A. Section on Preventive and Industrial Medicine and Public Health and Section on Pediatrics. Participating were Hart E. Van Riper, moderator, Jonas E. Salk, Thomas D. Dublin, Thomas Francis Jr., and Leonard A. Scheele. The discussion following the presentation of reports by Salk, Dublin, Francis and Scheele was to be opened by Aims C. McGuinness, Joseph Stokes Jr., and Albert B. Sabin.

After the meeting several papers were received from this joint session, and these are published in this issue of THE JOURNAL. In addition there is a second paper from Leonard A. Scheele that reveals some of the efforts made by the Public Health Service when questions on the usefulness and manufacture of the vaccine used in 1955 were raised. The discussion offered in written statements by Drs. Sabin and Stokes at the time of the meeting pertains to the papers offered at the panel discussion and not to the additional paper by Dr. Scheele. There also is included in this issue a series of questions and answers. The questions are from those raised by the audience of the joint A. M. A. section meeting, and the answers were given and subsequently edited by the members of the panel under the direction of the moderator, Dr. Van Riper.

There probably has not been any medical announcement during this century that has precipitated the discussion and controversy that followed the presentation of the Francis report in Ann Arbor on April 12. Because of the emotional impact of poliomyelitis on the average lay family one can realize how the public responded. At the same time there was a response, not so favorable, from many scientists who claimed such an announcement should have been made first in the usual way that matters of medical scientific importance are released. Also raised were questions by statisticians and epidemiologists. Then, when there appeared the first reports of poliomyelitis following the use of the vaccine the situation really became confusing. Charges and countercharges arose; accusations and counteraccusations followed.

During this period the Board of Trustees and members of the staff of the American Medical Association followed events closely, seeking scientific information for the doctors and their patients. Much that was learned was confidential, and much that was heard was rumor. There were many facts, but often they were shrouded from view by lack of information, sometimes by emotionally tinged presentations. As was pointed out earlier in THE JOURNAL, the Association had indicated its willingness to be helpful, but not much came of the offer. Thus the facts had to be gathered, sorted, and evaluated independently, a task not yet completed. Up to the present time the Association has not issued a statement on the efficacy and use of the vaccine, although it has commended those who have aided in the development of measures intended to control poliomyelitis. There are questions still needing answering, and the Association is continuing its study. In the meantime THE JOURNAL presents the papers offered at the A. M. A. meeting and other additional material for the information they contain.

APPLICATIONS OF MODERN GENETICS

In a review of the accomplishments of modern genetics, Glass [1] points out that in common with other scientists the geneticist possesses the power to effect great changes in the modern world but not the wisdom to evaluate the long-range effects of these changes or to direct the changes in ways that will ultimately produce the best results. In many respects there is no general agreement on the definition of these best results. A simpler problem arose during World War II when it was necessary to find a way to produce penicillin on a large scale. Strains of Penicillium giving a high yield of the antibiotic would grow only on the surface of the culture medium until geneticists produced a mutant by means of irradiation that would grow well throughout the medium. Geneticists also warned but in vain against the production of antibiotic-resistant strains of pathogens before such strains were actually produced. Now faced with a rapidly increasing world population, they are exploring ways of improving the nutritional value of plants and animals used for food. The production a few years ago of hybrid corn is a notable example.

Although the most fascinating phase of genetic study is the improvement of human stock, no means for accomplishing this has as yet been devised. One of the chief difficulties lies in the fact that a large proportion of the genes present in a given person are not manifest and that most characteristics of social significance depend on multiple genes. They are, therefore, rarely inherited *in toto* but when present represent a contribution of genes from both parents. The more genes involved in the transmission of a characteristic the less chance that it will be transmitted to one's offspring intact. Furthermore, a certain gene that in most combinations has a good (or bad) effect may in a certain rarer combination

1. Glass, B.: Genetics in the Service of Man, Johns Hopkins Mag. 6:2-16 (Feb.) 1955.

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have the opposite effect, or, as Glass puts it, "the geneticist can scarcely appraise the absolute . . . effect of a gene; it must be judged by the company it keeps." Physical traits are most nearly determined by heredity, but we inherit only certain potentialities. These can be realized only within the limitations of the environment. Mental traits are more modifiable by the environment than physical traits, and social traits or personality, although affected by heredity, are altered by environment with the greatest ease.

Advances in medical science have aided in the preservation and hence propagation of persons with such recessive genes as those giving a tendency to diabetes, myopia, various allergies, and certain types of deafness. The proportion of such persons in our civilization is increasing. Thus medical science increases the burden it must carry, because in the past many of these persons would have died in childhood or have been so handicapped socially as never to have married. Some of the measures advocated to prevent degradation of human stock include segregating the sexes to prevent propagation of institutionalized mentally defective persons, sterilization of such persons by ligating the spermatic ducts or the oviducts, and enacting laws against consanguineous marriages. None of these have made more than a feeble impression on the problem as a whole.

The more positive approach to the betterment of human kind, involving selective breeding of one type or another, is not likely to gain wide acceptance because of the violent emotional reactions such proposals automatically arouse. Aside from these emotional objections, Glass warns that the widespread use of a "perfect" donor through artificial insemination might lead to too great a uniformity in a world where diversity is still highly desirable. Furthermore, because harmful genes are hidden, a widely used donor might spread bad genes throughout a large segment of the population before they could be detected. This very thing has happened in the breeding of cattle by artificial insemination. As has been learned in certain royal families in the past, inbreeding brings recessive genes out into the open. If these are harmful, as they are more often than not, inbreeding will increase the number of persons afflicted. It may be concluded that it is easier to define good environment than good heredity. So far, the power to change man genetically exceeds the wisdom needed to know in what direction genetic controls should be applied for best results.

BLOOD FOUNDATION

Elsewhere in THE JOURNAL (page 1284) is a report of the Committee on Blood of the American Medical Association that tells the story of the creation of the Blood Foundation. The creation of this foundation was an important step and reflects the untiring efforts by A. M. A. representatives and others over a long period of time. While the Association has been interested in blood-banking programs for some years, it was in 1953 that the House of Delegates adopted a resolution recommending the establishment of a coordinated national blood program organized by the American Medical Association, the American National Red Cross, and other qualified organizations such as the American Hospital Association, the American Society of Clinical Pathologists, and the American Association of Blood Banks.

There are certain basic principles regarding the supply of blood, its storage and use that are mentioned in the report (page 1284). These are important, but perhaps of no less significance is the fact that the program of the Blood Foundation is voluntary. Therefore its success will depend on the degree of cooperation it will receive from those responsible for the blood-banking facilities in this country. There are many problems to be solved, and solutions may not always come easily; however, one can look with hope to the future in view of the stature of the organizations behind this foundation. Of great importance was the selection of the officers and directors of the Blood Foundation, and the men chosen reflect admirably the energy and leadership provided during the foundation's period of development. The doctors of America can hope to hear much about this comparatively new body in which they should be vitally interested.

MILD POLIOMYELITIS

A recent press release from the health department of the state of New York asks physicians to be watchful for "a non-paralytic polio-like illness." The department reported outbreaks of the disease in several areas within the state. This warning is timely. Such outbreaks have been observed elsewhere and have been commented on repeatedly by members of the Chicago health department. Apparently they are very common in this area, and it is not unusual to learn of a child who developed mild poliomyelitis after a history of playing with other children in his neighborhood but who suffered nothing more than the symptoms seen with a cold or mild intestinal upset. Unless one is on the alert for such histories the disease may be missed and an inaccurate diagnosis made. In fact, the intestinal upset has led to surgery within the abdomen, just as missed instances of pneumonia in the past have resulted in the removal of appendixes.

The press release from New York reads in part: "While the disease has symptoms very similar to those of poliomyelitis, it is very mild, with no paralysis, and recovery is generally within a few days. It occurs most frequently among young children and tends to affect a large number of persons in the same family. . . . The disease is characterized by headache, fever and nausea with moderate stiffness of the neck, an increased number of cells in the spinal fluid and occasional sore throat. Occasionally it has been accompanied by the symptoms of epidemic pleurodynia, or pains in the chest, and, rarely, by sores in the mouth suggesting herpangina."

The request from New York for information from physicians might well be heeded elsewhere in the country if this illness is prevalent. And as for prevalence, one needs only to keep in mind the attitude of a well-known epidemiologist who claims that poliomyelitis during the season is as prevalent as measles during an outbreak of this disease.

ORGANIZATION SECTION

BLOOD FOUNDATION

The Committee on Blood of the American Medical Association has authorized publication of the following report.

The incorporation of the Blood Foundation and the first meeting of its board of directors on May 7 of this year brought to a successful culmination the efforts of the Committee on Blood of the American Medical Association to join together the various voluntary organizations with major interests in the supply of blood and in blood banking. These attempts had their inauguration in June, 1948, when the House of Delegates authorized the Board of Trustees to appoint a liaison committee for the American Red Cross blood-banking program. The name of this committee was subsequently changed to the Committee on Blood Banking at the 1949 meeting and later to the Committee on Blood in December, 1952. The activities of the Committee were spurred by the action of the House of Delegates of the American Medical Association in passing the California resolution in 1953, which recommended the establishment of a coordinated national blood program organized by the American Medical Association, American National Red Cross, and other qualified organizations interested in blood banking.

The events leading up to this decision on the part of the House of Delegates can actually be traced back prior to World War II. At that time blood banking had been established as a practical procedure but most blood banks were operated in conjunction with large hospitals or medical schools. In many cities blood transfusions depended largely upon the existence of a pool of professional donors. Even before Pearl Harbor it was realized that if the country were to be properly prepared for emergency then blood procurement on some nationwide basis would be necessary. From discussions between the Army, Navy, National Research Council, and American National Red Cross a plan for an American Red Cross Blood Donor Service emerged on Feb. 4, 1941. Ten months later the United States was plunged into war and the demand for whole blood and plasma suddenly expanded into a real problem in logistics for the armed forces. Red Cross Blood Donor Centers were established in 35 cities, and 63 mobile units visited other areas on a prearranged schedule; between them these facilities drew a total of 13,326,242 pt. of blood during World War II.

REGIONAL BLOOD BANK PROGRAM

With peace in 1946 the Red Cross abandoned its war-time program of blood collection. Although new blood banks were established in many communities, others returned to the old system of reliance upon professional donors. Physicians trained by service in the armed forces to the ready availability of plasma and whole blood desired similar supplies for their civilian practice. Many chapters of the Red Cross urged reestablishment of the Red Cross system of collection for voluntary donors. In 1947 representatives of the Red Cross appeared before the Board of Trustees of the American Medical Association relative to the establishment of a national blood program by the Red Cross. The proposed program was to establish a system to furnish whole blood and blood derivatives throughout the country. The Board of Trustees agreed to recommend approval in principle of the Red Cross plan for the establishment of a national blood program with the understanding that the operation should be maintained on a community level with the approval of the county medical societies concerned. The matter was referred to the House of Delegates, and the action of the Board was affirmed by the House of Delegates in June of that same year. Launching of this program by the Red Cross created many unseen problems requiring a considerable degree of attention, exercise of diplomacy, and formulation of principles and policy by the Board of Trustees, the A. M. A. Committee, and the House of Delegates. Criticism of the Red Cross Regional Blood Bank program came from many sources; after considering these criticisms in June, 1948, the House of Delegates reaffirmed its previous action of approval but defined what was meant by approval in principle in the following words:

"Realizing the possibility of a national emergency requiring large amounts of blood in the treatment of civilian and military casualties and realizing the unique position of the American Red Cross in disaster relief, your committee is of the opinion that no change should be made at this time in the 'approval in principle' of the participation of the American Red Cross in the national blood program voted at the Interim Session in January 1948.

"However, your committee would call attention of the House to the fact that long before the Red Cross entered this field of medical practice many previously established blood banks had been operating successfully and adequately under strictly local supervision and had rendered invaluable services to the community. To disturb such independent local units would, in the opinion of your committee, be unwise and disastrous, for they have repeatedly demonstrated their ability to meet local and regional needs. Furthermore, they have demonstrated the practicability of free enterprise and local initiative.

"From the testimony presented at the several hearings before your reference committee, it is quite evident that there has been confusion and misunderstanding between local chapters of the Red Cross and the medical profession at local levels.

"It is the opinion of your reference committee that the 'Approval in Principle' be construed as follows: First, local control must be by the county medical society. Second, the local medical society should be the initial contact in the contemplation of inauguration of a new blood bank. Third, no publicity nor news releases shall be released except by mutual consent of the local county medical society and the local chapter of the American Red Cross. Fourth, difference of opinion in establishment or operation of a blood bank in either administrative or technical detail shall be arbitrated at state levels by joint committees from the state medical society and the American Red Cross."

PRINCIPLES REGARDING BLOOD SUPPLY AND BANKING

In the period between the formation of the liaison committee in 1948 and the formation of the Blood Foundation in 1955, the Board of Trustees on recommendations from the Committee on Blood has requested the House of Delegates to adopt certain basic principles regarding the supply of blood and blood banking: 1. The primary interest of physicians in relation to blood and blood banking is to secure the widest, most efficient and economical supply of safe usable blood and its derivatives for the American people. 2. In establishing blood-banking systems the principle of local determination by county medical society endorsement is desirable. 3. Blood replacement responsibility is regarded as a problem of the family of the recipient, his friends, and various organizations of which he is a member, as well as the community. 4. The interbank exchange of blood on a unit-for-unit basis is felt necessary to develop an integrated national system of blood banks. 5. Nonprofit operation of blood banks but with service cost borne by the patient has been repeatedly emphasized. Possibly restatement of the words used in the June, 1952, report accepted by the House of Delegates will be most clarifying: "Since blood is derived from human beings only, our aim should continue to be directed at having no profit from trafficking in whole blood itself; however, all services rendered cost something and are paid for by or on behalf of every recipient of such services. The service charge should cover all costs of the operation including depreciation and expansion reserves, but the realization of profit for the support of other institutional needs should be discouraged."

In the formulation of the bylaws of the Blood Foundation the Committee on Blood has fought for and has succeeded in having included all of the principles adopted by the House of Delegates with but one modification. While the unit-for-unit exchange of blood between blood banks is accepted as the principle, it is recognized that because of the perishable nature of blood there is a certain percentage of loss in all blood banks. The larger the blood bank the lower this percentage of loss would be, although there is an irreducible minimum. Smaller

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blood banks because of their lesser volume and because of the necessity for maintaining a supply of all types of blood encounter a larger percentage loss. Therefore it was recognized by the board of directors of the Blood Foundation that some adjustment must be made in the system of unit-for-unit exchange because replacement of a borrowed unit of processed blood to a small bank by a larger bank actually involves less investment on the part of the large bank. This matter is presently under consideration by a special committee appointed by the president of the Blood Foundation.

PROGRAM

The program of the Blood Foundation is entirely voluntary and its success or failure will depend upon the degree of cooperation it will receive from the blood-banking facilities of the United States. There are many attendant problems to be solved by the board of directors in this trying, occasionally vexing, new field.

The leadership furnished by the Committee on Blood in these negotiations with the American National Red Cross, American Hospital Association, American Society of Clinical Pathologists, and American Association of Blood Banks is probably best attested to by the fact that the Chairman of the Committee on Blood, Dr. Leonard Larson, has served as chairman of the joint negotiating committees and has now been elected the first president of the Blood Foundation. This in no way should be construed as deprecation of the efforts of the representatives of the American National Red Cross, the American Hospital Association, the American Society of Clinical Pathologists, and the American Association of Blood Banks. All representatives during these meetings have exhibited high-minded principle and an earnest desire to negotiate a workable solution to the problems of blood banking. Acknowledgment too should be made to former members of the Committee, Drs. William A. Coventry, James Q. Graves, James Stevenson, and especially the former co-chairman Herbert Ramsey for their devoted unselfish service.

Officers and directors of the Blood Foundation are Leonard W. Larson, M.D., president; Merlin L. Trumbull, M.D., vice-president; Karl S. Klicka, M.D., treasurer; and David N. W. Grant, M.D.; Donald H. Kaump, M.D.; Walter B. Martin, M.D.; James J. Griffitts, M.D.; Mr. Charles H. Kellstadt; Edwin L. Crosby, M.D.; and Frank W. Konzelmann, M.D.

NEW TELEVISION PROGRAM ON MEDICAL RESEARCH

"Medical Horizons," a new half-hour television series, presented by Ciba Pharmaceutical Products, Inc., in cooperation with the American Medical Association, will be premiered on Monday evening, Sept. 12, over ABC-TV. The new documentary series will present specific accomplishments in the field of medicine brought about by the teamwork of modern medical research, education, and practice. The program will be presented each Monday from 9:30 to 10:00 p. m., New York time, on a network of 45 ABC-TV affiliated stations for a minimum of 26 weeks. Stations in the Pacific and Mountain time zones will receive the program on a two-week delayed basis via Kinescope film. Emanating via live remote telecasts from medical institutions and research centers, the series will be packaged by the J. Walter Thompson Company under producer-director Fred Carney. "Medical Horizons" will be under the supervision of Dr. William T. Strauss of Ciba.

DR. WERMER LEAVES FOR NEW POST

Dr. Paul L. Wermer, who has been with the A. M. A. during the past six years as Secretary of the Committee on Research and the Committee on Blood, left July 15 to take a position as vice-president and director of product development for Warner-Chilcott Laboratories, Morris Plains, N. J. As Secretary of the Committee on Research, Dr. Wermer assisted in studies of breast cancer, worked on various studies in connection with diabetes and pregnancy, and established a registry for blood dyscrasias; he presently is engaged in setting up a registry for reporting toxic reactions to therapeutic agents.

FEDERAL MEDICAL LEGISLATION

First Session, 84th Congress

National Hospital Week

Senator Hill (D., Ala.) and Senator Thye (R., Minn.), in S. Con. Res. 23, and Congressman Priest of Tennessee, in H. Con. Res. 113, would have Congress request the American people to "cooperate in a voluntary effort to observe National Hospital Week." These measures were referred favorably and passed and signed by the President. These bills were handled in the Senate by the Committee on Public Welfare and in the House by the Interstate and Foreign Commerce Committee.

Federal Aid to State Soldiers' Homes

Congresswoman Rogers (R., Mass.), in H. R. 5378; Congressman Ford (R., Mich.), in H. R. 5564; Congressman Forand (D., R. I.), in H. R. 5930; Senator Langer (R., N. D.), in S. 1780; and Senator Green (D., R. I.), in S. 1916, propose to require that at least one-half of the beds of each state soldiers' home be available for domiciliary care, if federal subsidies are obtained. The Senate measures were referred to the Committee on Labor and Public Welfare, the House measures to the Committee on Veterans' Affairs and the Committee on Armed Services.

Graduate Traineeship for Nurses

Congressman Bolton (R., Ohio), in H. R. 648, would authorize the surgeon general of the Public Health Service to provide traineeships for graduate professional nurses for training to teach in the various fields of nurses' training or to serve in an administrative or supervisory capacity in the various fields of nursing. This bill was referred to the Interstate and Foreign Commerce Committee.

Veterans Chiropractic Treatment

Senator Magnuson (D., Wash.), in S. 1768, proposed to extend chiropractic treatment through the Veterans Administration to veterans. His bill states: "That whenever any person is entitled by law or regulation to receive medical care by or through the Veterans' Administration, he shall, if he so elects, have the right to receive chiropractic care and the Chief Medical Director shall make available the services of qualified chiropractors." This bill was referred to the Committee on Labor and Public Welfare.

Lengthening Presumption of Service Connection for Arthritis, Psychoses, and Multiple Sclerosis

Congressman Henderson (R., Ohio) has introduced, in H. R. 5719, a measure that would "amend the Veterans' Regulations to provide that arthritis, psychoses, or multiple sclerosis developing a 10 per centum or more degree of disability within three years after separation from active service shall be presumed to be service-connected." The present presumption period for arthritis is one year, for psychoses two years, and multiple sclerosis two years. This measure was referred to the Veterans' Affairs Committee.

Presumption of Service Connection for Holders of Purple Heart

Congressman Siler (R., Ky.), in H. R. 5667, would amend the Veterans' Regulations to provide that "if a person has been awarded the Order of the Purple Heart and is not otherwise suffering from a service-incurred or service-aggravated disease or disability, 10 per centum or more in degree, he shall be deemed to be suffering from such a disease or disability, 10 per centum in degree." This would apply only to persons with the Order of the Purple Heart after the enactment of the proposed legislation. This bill was referred to the Committee on Veterans' Affairs.

Practical Nurse Training

Congressman Huddleston (D., Ala.) has introduced an identical measure with S. 929, reported in THE JOURNAL, April 30, 1955, page 1618. This will amend the Vocational Education Act to establish a training program for practical nurse and auxiliary personnel under the Commissioner of Education in the Department of Health, Education, and Welfare. This bill was referred to the Committee on Education and Labor.

Prepared by the Washington Office of the American Medical Association.

MEDICAL NEWS

CALIFORNIA

Physicians' Orchestra.—A Physicians' Symphony Orchestra is being organized in San Francisco under the conductorship of Mr. Murray Graitzer. The first meeting was held in the auditorium of the San Francisco Medical Society's headquarters June 7. For information, call Dr. Charles P. Lebo, YUkon 6-4370.

Health Department Needs Physicians.—The Los Angeles City Health Department announces the availability of two administrative posts for physicians with public health experience and several positions in clinical medicine. Applications are being received by the commissioners of the board of health for the position of medical director, a post involving the direction of communicable disease control, maternal and child health, adult health, laboratories, and public health nursing. Salary range is from $797 to $992 a month. The department is seeking also a qualified epidemiologist with formal training in public health, special experience in communicable disease control, and administrative abilities. This position pays $715 to $889 a month. Openings for chest specialists for clinical duties in the tuberculosis control service are available at salaries ranging from $608 to $755. None of these positions requires a competitive Civil Service examination. Applicants will be interviewed and appointed on the basis of training, background, and ability. For information, qualified physicians may contact Dr. Hamlet C. Pulley, Executive Officer, Los Angeles City Health Department, 111 E. First St., Los Angeles 12.

CONNECTICUT

State Medical Election.—The Connecticut State Medical Society recently elected Drs. Oliver L. Stringfield, Stamford, president; Ralph T. Ogden, Hartford, president-elect; John D. Booth, Danbury, first vice-president; John F. Kilgus, Litchfield, second vice-president; and reelected Drs. Creighton Barker, New Haven, executive secretary; Frank H. Couch, Cromwell, treasurer; and Stanley B. Weld, Hartford, editor of the *Connecticut State Medical Journal*. At a special ceremony during the annual dinner, 50-year pins were awarded to Drs. David R. Lyman, Wallingford, Harry C. Clifton, West Hartford, and Irwin Granniss, Northford.

IDAHO

Rheumatic Fever Program.—A $100,000 free penicillin program to curb rheumatic fever in Idaho was recently approved by the Idaho Heart Association and Idaho State Department of Public Health, which will share the costs equally and provide tablets to physicians for use in the medically indigent. The action was taken at the annual scientific assembly of the Idaho Heart Association, where the following officers were elected for the coming year: Dr. Harvey A. Hatch, Idaho Falls, president; Dr. Luther C. Thompson, Twin Falls, president-elect; Dr. Joseph Saltzer, Nampa, vice-president; Dr. Paul R. Sharick, Boise, secretary; and Mr. William A. Goodall, Boise, treasurer.

ILLINOIS

Personal.—Dr. Werner Tuteur, clinical director at Elgin State Hospital, Elgin, has been given a grant-in-aid of $3,000 by Smith, Kline and French Pharmaceutical Company, to investigate further possibilities of Thorazine and reserpine on highly disturbed psychotic patients.

Epilepsy in Industry.—The Illinois Epilepsy League has initiated a drive to encourage wider employment of persons with epilepsy through its sponsorship of an Industry Committee for Employment, consisting of industrialists, business men, and the press. At an Epilepsy in Industry Conference in Chicago on May 24, a panel discussion, "The Nature of the Problem," was presented by Dr. Frederick W. Stamps, University of Illinois, Chicago, who discussed the medical aspects; Dr. Edward D. Schwade, Milwaukee, who covered the social and medicolegal phases; and Miss Virginia Gibson, of the Division of Services for Crippled Children of the State of Illinois, who related the problem to public health. At the luncheon session the Hon. Maxwell M. Rabb, Washington, D. C., Secretary to the President's Cabinet, stressed the social and economic importance of providing job opportunities for rehabilitated workers with chronic disorders or other handicaps, and Dr. Abe B. Baker, Minneapolis, chairman of the Committee for Research in Neurological Disorders, explained the process of restoring the neurologically disabled to productivity. The afternoon session was devoted to employment, with a panel discussion of "Epilepsy in Industry," in which Dr. Frederic A. Gibbs of the Consultation Clinic on Epilepsy at the University of Illinois, Chicago, and Dr. Joseph H. Chivers, medical director of the Crane Company, Chicago, spoke on medicine and on industrial medicine respectively. Dr. William G. Lennox, Boston, was cited for a lifetime of teaching, research, and leadership in epilepsy. Dr. Nicholas P. Dallis, Toledo, Ohio, who recently devoted many weeks to a dramatic exposition of epilepsy in his syndicated comic strip, "Rex Morgan, M.D.," was named for his outstanding contribution to public education.

Chicago

Alumni Honored.—At the annual alumni dinner of the Medical Alumni Association, University of Chicago School of Medicine, June 9, Dr. Russell M. Wilder, Rochester, Minn., was presented with the Gold Key of the Medical Alumni Association, and Dr. Paul C. Bucy, Chicago, and Dr. David Bodian, Baltimore, received Distinguished Service awards.

Plastic Surgery of Head and Neck.—The American Otorhinologic Society for Plastic Surgery announces its second graduate course in plastic surgery of the head and neck Oct. 7-9 at the Morrison Hotel. The course will be limited as to the number of participants, who will be recognized surgeons specializing exclusively in otolaryngology, ophthalmology, and plastic surgery of the head and neck. For information, write Dr. Louis Joel Feit, Secretary, 66 Park Ave., New York 16.

New Vice-President at University.—Herbert E. Longenecker, Ph.D., dean of the graduate school at the University of Pittsburgh since 1946, has been appointed vice-president of the University of Illinois in charge of the Chicago Professional Colleges to fill the post vacant since July, 1953. Dr. Longenecker will be administrative head of the university's colleges of medicine, dentistry, and pharmacy, graduate college in Chicago, school of nursing, research and educational hospitals, clinics, institutes, and other health science units at the West Side Medical Center. Dr. Longenecker served as a graduate assistant and later as an instructor in Pennsylvania State College from 1933 to 1936; National Research Council Fellow at the University of Liverpool, England, from 1936 to 1937, University of Cologne, Germany, in 1937, Queen's University, Canada, in 1938; and then came to the University of Pittsburgh, where his posts have included a professorship of biochemistry and a directorship of the Buhl Foundation Project.

IOWA

Series of Medical Forums.—A series of five medical forums was recently presented in Davenport under the joint sponsorship of the Scott County Medical Society and Davenport Newspapers, Inc. The opening and closing meetings were "for women only" sessions, and the others dealt with problems of dentistry, psychiatric treatment, and heart disease. About 2,000 women attended

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

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the closing session, at which Dr. Walter J. Balzer served as moderator for a panel that included Drs. Arline M. Beal, Walter E. Foley Jr., Merrill M. Benfer, and Howard A. Weis, Davenport. The Iowa State Medical Society presented the newspapers with its first Community Service awards. A second series of health forums is projected.

KANSAS

Compensation Law Amended.—The Kansas Workmen's Compensation Law has been amended to provide treatment of an injured workman in the total amount of $2,500 and extension of the 120 day limitation on medical treatment for a longer period of time in extreme cases, at the discretion of the commissioner. The amendment provides also that the unreasonable refusal of the workman to submit to an operation for surgical repair of a traumatic hernia shall deprive such workman of any benefits under the act, except that in the event such hernia is inoperable, compensation shall be paid at the rate of 60% of the average weekly wage during 12 weeks. The physician examining an employee for an employer is required to furnish said employee, on request, and within 15 days after such examination, with a copy of the identical medical report furnished the employer.

MAINE

State Medical Election.—Newly elected officers of the Maine Medical Association include Dr. Martyn A. Vickers, Bangor, president; Dr. Armand Albert, Van Buren, president-elect; and Esther M. Kennard, Portland, secretary-treasurer.

Audiology for Industry.—Colby College, Waterville, will present the third annual Course in Industrial Deafness Aug. 7-13. The course, which will be given for 20 participants, will train personnel in conducting conservation of hearing programs in noisy industries. Dr. Frederick Thayer Hill will be director of the course. Registrants will live on the college campus. Tuition fee of $200 includes board and room. Applications should be made to Mr. William A. Macomber, Director, Division of Adult Education and Extension, Colby College, Waterville.

NEW YORK

Academy of Preventive Medicine.—The New York State Academy of Preventive Medicine was organized at a meeting in Buffalo May 11. Dr. Vivian A. Van Volkenburgh, Albany, was elected president; Dr. Franklin M. Foote, New York, president-elect; Dr. Morton L. Levin, Albany, vice-president; Dr. Walter C. Levy, Albany, secretary-treasurer; and Drs. Joseph H. Kinnaman, Garden City, Michael Antell, New York, and Milton Tully, Hornell, directors for three year, two year, and one year terms respectively. Membership is limited to physicians who are diplomates of the American Board of Preventive Medicine, residing or employed in New York State. Qualified applicants are eligible for charter membership by application until Dec. 31, 1955. After that date, eligible applicants can be elected to membership. Forms for charter membership may be secured from Dr. Walter C. Levy, Secretary-Treasurer, New York State Academy of Preventive Medicine, 353 Broadway, Albany.

Personal.—Dr. Freeman S. O'Brien has resigned as health officer of the village of Wappingers Falls because of ill health, and Dr. Albert R. Scafuri, assistant health officer during the recent absence of Dr. O'Brien, has been appointed health officer.——Dr. Giles F. Filley, formerly director of the department of physiology, Trudeau-Saranac Institute, Trudeau, will join the department of medicine at the University of Colorado Medical Center, Denver, Sept. 1. Dr. Filley will also serve as clinical physiologist at the Colorado Foundation for Research in Tuberculosis.——Dr. James A. Halsted has been appointed chief of professional services at the Veterans Administration Hospital, Syracuse, and associate professor of medicine at the State University of New York College of Medicine at Syracuse. He was formerly a member of the staff at the Veterans Administration Hospital in Los Angeles and at the faculty of the University of California at Los Angeles Medical Center.——Dr. C. Stuart Welch, associate professor of surgery, and Dr. Ralph D. Alley, instructor in surgery, Albany Medical College, read papers on new advances in surgery before the third Medical Society Congress, held in Rabat and Casablanca, Morocco, April 12-16, under the sponsorship of the Morocco Medical Society.

New York City

Appointments for Dr. Sheehan.—Dr. Donal Sheehan, acting director of the New York University-Bellevue Medical Center since 1951, was recently named dean of the College of Medicine and of the Postgraduate Medical School and deputy director of the medical center—duties that had been shared by Dr. Currier McEwen, dean of the medical college, and Dr. Robert Boggs, dean of the Postgraduate Medical School. Dr. Sheehan assumed his new responsibilities on July 1, when, at his own request, Dr. McEwen returned to teaching and Dr. Boggs' resignation became effective. Dr. Sheehan was acting dean from 1943 to 1945.

Gift for New Library.—An anonymous gift of $100,000 has been made for the new library at New York Medical College, Flower and Fifth Avenue Hospitals. The library, part of the six-story building being constructed on 105th Street off Fifth Avenue by the college as the first step in the million dollar expansion program, will replace the present medical library on the second floor of the college building on Fifth Avenue and 106th Street. The library will be integrated with the Flower-Fifth Avenue Hospital record library, so that clinical studies can easily be made of case histories in conjunction with textbooks and medical journals. The hospital case histories will be on microfilm. A room will be set aside in the library for audiovisual aids, including a microfilm projector, motion picture projector and screen, lantern slides, and tape recorders. A periodical room and a second study room will complete the library.

OHIO

Course on Occupational Skin Problems.—The Institute of Industrial Health of the University of Cincinnati announces that the course of instruction in occupational skin problems will be presented Oct. 10-14. The program will be divided into three daily sessions—morning lectures and clinical demonstrations, afternoon field instruction in industrial plants, and evening panel discussions. Physicians interested in attending the course should write to Secretary, Institute of Industrial Health, Kettering Laboratory, Eden and Bethesda avenues, Cincinnati 19. Attendance will be limited.

Personal.—Dr. Walter J. Zeiter, assistant to the executive director of the Cleveland Clinic Foundation, was recently named medical coordinator, with the responsibility of coordinating the medical and surgical services with the administrative departments. Dr. Zeiter, who is president of the National Association of Clinic Managers, joined the staff of the Cleveland Clinic Foundation in 1937 as head of the department of physical medicine and rehabilitation and established the foundation's training school for physical therapists. He has been a member of the A. M. A. Council on Physical Medicine and Rehabilitation since 1951.

TEXAS

Chauncey Leake Goes to Ohio State.—Chauncey D. Leake, Ph.D., executive director, University of Texas Medical Branch at Galveston, has been appointed assistant dean of the college of medicine and professor of pharmacology at Ohio State University, Columbus. Dr. Leake has been at the Texas Medical Branch since 1942, when he was named vice-president. He will assume his new duties Sept. 1, succeeding Dr. John A. Prior, who asked to be relieved of this position to devote full time to teaching, research, and patient care in the department of medicine in which he is a professor and director of the division of chest diseases. Dr. Leake has taught physiology and pharmacology at the University of Wisconsin in Madison and at the University of California, Berkeley-San Francisco, where he served as lecturer in medical history and librarian of the medical school. He is on the editorial board of the *Archives of International Pharmacology* and is chairman of the committee of problems of alcohol of the National Academy of Sciences.

WASHINGTON

Course in Paralytic Respiratory Failure.—A postgraduate course in the Management of Acute Paralytic Respiratory Failure will be presented at the University of Washington School of Medicine, Seattle, Aug. 19. Treatment methods for poliomyelitis, polyneuritis, nervous system poisoning, and related disease states will be discussed and new equipment demonstrated. Dr. Russell R. de Alvarez, professor of the department of obstetrics and gynecology, will serve as chairman for the course, which will be sponsored by the University of Washington School of Medicine, Washington State Medical Association, Washington State Department of Health, and by a grant from the National Foundation for Infantile Paralysis. The course (fee, $10) is open to graduates of medical schools approved by the Council on Medical Education and Hospitals of the American Medical Association. Checks made payable to the University of Washington should accompany the application and be addressed to the Division of Postgraduate Medical Education, University of Washington School of Medicine, Harborview Hospital Annex, 325 Ninth Avenue, Seattle 4.

WEST VIRGINIA

Personal.—Drs. Walter L. Barbour, Whitesville, Merwin B. Moore, Huntington, and Ozro H. Bobbitt, Charleston, have been elected to honorary life membership in the West Virginia State Medical Association.

State Medical Meeting.—The West Virginia State Medical Association will hold its annual meeting Aug. 18-20 at the Greenbrier, White Sulphur Springs, under the presidency of Dr. James P. McMullen, Wellsburg. The convention will be preceded by the Freedom of Information Clinic Wednesday evening. The clinic, with its six member panel, composed of representatives of the press and the medical profession, and its audience participation, supplants the public relations meeting customarily held. It will be addressed by Mr. Leo E. Brown, Chicago, A. M. A. Director of Public Relations, and Mr. Peyton B. Winfree Jr., executive editor of the *News and Advance*, Lynchburg, Va. All general sessions will be held in the theater of the newly completed air-conditioned convention unit. Sound motion pictures on scientific subjects will be shown each morning at 8:15. The convention will open Thursday at 9:15 a. m. The following symposium on hypertension will be presented by members of the faculty of Duke University School of Medicine, Durham, N. C.:

Etiology and Surgical Treatment of Hypertension, Keith S. Grimson.
Pharmacology of Drugs Used in Hypertension, James P. Hendrix.
Medical Therapy of Hypertension, Edward S. Orgain.

A panel discussion and question and answer period will follow the symposium. Dr. Robert U. Drinkard Jr., Wheeling, will serve as moderator at this session. The following program is scheduled for Friday morning, with Dr. Richard E. Flood, Weirton, as moderator:

Present-Day Problems Concerned with Antibiotic Therapy, Chester S. Keefer, Boston.
Differential Diagnosis of Hip Joint Disease in Children, Marcus J. Stewart, Memphis, Tenn.
Management of Intractable Peptic Ulcer, Charles M. Caravati, Richmond, Va.

The final general session, Saturday morning, will have as moderator Dr. Richard W. Corbitt, Parkersburg, who will preside over the following program:

Malignant Lesions of the Colon, Isidor S. Ravdin, Philadelphia.
Injuries of the Ureter and Bladder During Pelvic and Colon Surgery, John L. Emmett, Rochester, Minn.
The Anesthesiologist in the Medical-Surgical Team, Curtiss B. Hickcox, Hartford, Conn.

The section on urology has scheduled a symposium for Friday afternoon, when guest speakers will be Dr. Elmer Hess, Erie, Pa., President of the American Medical Association, and Dr. John L. Emmett, professor of surgery at the Mayo Foundation Graduate School of the University of Minnesota, Rochester. Dr. Hess will also address the final meeting of the house of delegates Saturday, 3:30 p. m. His subject will be "Medical Crisis." Dr. Isidor S. Ravdin, Philadelphia, guest speaker at the meeting of the section on surgery Friday afternoon, will discuss "Gastric Ulcer and Gastric Cancer," and the guest speaker at the meeting of the section on orthopedic surgery, which will be held simultaneously, will be Dr. Marcus J. Stewart, Memphis, Tenn., who will have as his topic "Treatment of Fractures of the Hip with Non-Union."

Numerous social events have been planned. These will include the annual cocktail party, which will be given under the sponsorship of the Kloman Instrument Company, Inc., of Charleston, Saturday, 7:30 p. m.; and a "Gay Nineties" party, which has been arranged by the Woman's Auxiliary for Friday, 10 p. m. An innovation of the annual golf tournament will be a separate tournament for guest physicians and representatives of technical exhibits.

WYOMING

State Medical Election.—The Wyoming State Medical Society recently elected Dr. Russell I. Williams, Cheyenne, president; Dr. Joseph S. Hellewell, Evanston, president-elect; Dr. Harlan B. Anderson, Casper, vice-president; Dr. Benjamin Gitlitz, Thermopolis, secretary; and Dr. Carleton D. Anton, Sheridan, treasurer.

GENERAL

Cancer Research Project.—A joint attack on malignant melanoma has been organized between the University of Texas M. D. Anderson Hospital and Tumor Institute in the Texas Medical Center, Houston, and the University of Oregon Medical School, Portland. The "Melanoma Study Section," organized in December, 1954, is the second such research group organized by the University of Texas M. D. Anderson Hospital. The first was the "Cancer Eye Study Section," for the study of squamous ocular carcinoma in cattle. The National Cancer Institute has recommended approval of grants for the study section.

Heart Sound Tape Library.—A library of tape-recorded heart sounds and murmurs is being established by the American Heart Association for use in undergraduate and postgraduate medical education. The association's committee on auscultatory phenomena announces that the library will include 10 teaching reels and 34 different heart sounds and murmurs available in loop form at 1⅞ and 7½ in. per second. The tapes are expected to be ready for circulation around Sept. 1. Information on use of the tapes, as well as descriptive materials on their content, can be obtained from the Medical Division, American Heart Association, 44 E. 23rd St., New York 10.

The Lalor Foundation Awards.—The Lalor Foundation (4400 Lancaster Pike, Wilmington, Del.) announces awards up to $1,100 each to 23 faculty members of American and Canadian colleges and universities for 1955 summer research and study in the biological sciences. The Marine Biological Laboratory at Woods Hole, Mass., has announced appointment of one Senior Lalor Fellow and six Postdoctorate Lalor Fellows for the summer of 1955 under its agreement with the Lalor Foundation. It is anticipated that announcement will be made in October regarding the next series of awards to be offered to college and university faculty members for research in the biological sciences during the summer of 1956.

Request Names of Multiple Sclerosis Victims.—A nationwide search is being conducted by some 2,750 JayCee chapters in cooperation with the National Multiple Sclerosis Society and its 70 chapters, to reach an estimated 250,000 unknown multiple sclerosis victims and put them in touch with the national society. Physicians and multiple sclerosis sufferers and their relatives are urged to advise the National Multiple Sclerosis Society of the names and addresses of all multiple sclerosis victims. The identity of any person reported to the society will be kept confidential. Dr. Hans H. Reese, Madison, chairman of the medical advisory board of the National Multiple Sclerosis Society, will provide information for physicians interested in the search for victims. Interest of the JayCees in the program stems primarily from the fact that the disease is reported to strike 1 in every 400 young adults. The JayCee age group is from 20 to 35.

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New Periodical on Alcohol Problems.—The International Institute for Research on Problems of Alcohol has announced that its official organ will be the *International Journal of Alcohol and Alcoholism*, which will be published three times annually. The new periodical will present surveys of the problems, achievements, and statistics of individual countries, beginning with surveys on Austria and Canada in the June issue. The journal will also feature current and classified bibliographies of the world literature. The journal will publish in English, French, German, Italian, and Spanish. The international subscription price is 30 shillings; in the U. S. A., $6. Editorial correspondence should be addressed to H. Pullar-Strecker, M.D., Wyke House, Isleworth, Middlesex, England. Business correspondence should be addressed to the publishers, Blackwell Scientific Publications, 25 Broad St., Oxford, England, or to the American publishers, Charles C Thomas, 301 E. Lawrence Ave., Springfield, Ill.

Cardiac Research Grants.—Applications by scientific investigators for support of research to be undertaken during the year beginning July 1, 1956, are being accepted by the American Heart Association. The application deadline for research fellowships and established investigatorships is Sept. 15 and for grants-in-aid, Nov. 1. Established investigatorships are awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,000 to $9,000. Research fellowships are awarded to young men and women with doctoral degrees for periods of one to two years to enable them to train as investigators under experienced supervision (annual stipends, $3,500-$5,600). Grants-in-aid are made in varying amounts, not to exceed $10,000, to experienced investigators to provide support for specific projects. Career investigators are selected by the research committee, rather than by application. Information may be obtained from the Medical Director, American Heart Association, 44 East 23rd St., New York 10.

Radiological Conference.—The 17th Midsummer Radiological Conference of the Rocky Mountain Radiological Society will convene at the Hotel Shirley-Savoy, Denver, Aug. 18-20, under the presidency of Dr. Alfred M. Popma, Boise, Idaho. Guest speakers and their first presentations include:

Warren W. Furey, Chicago, The Radiologist—Quo Vadis?
Higdon B. Elkins, Iowa City, Use of Radioactive Gold Intra-Abdominally in the Treatment of Carcinoma of the Ovary.
George Z. Williams, Bethesda, Md., Effects of X-Ray on the Mechanism of Carcinogenesis in the Liver.
Isadore Meschan, Little Rock, Ark., Review of Cobalt 60 and Its Interstitial Uses.
John W. Hope, Philadelphia, Roentgen Fables of Infants and Children. Part I: The Unfilled Chest, the Bulgy Neck and the Shadowy Belly.

Single author presentations by invitation will include:

Semiconductors in the Field of Radiology, E. Dale Trout, Ph.D., Milwaukee.
Clinical Stationary Field Therapy with a Cobalt 60 Unit. Part I and Part II, Gilbert H. Fletcher, Houston, Texas.
Radiological Demonstration of Tumors of Sinuses and Nasopharynx, John P. McGraw, Houston, Texas.
Some Internal Abdominal Hernias, Cyrus W. Partington, Denver.
New Concept of Treatment of Breast Cancer, Bertram V. A. Lowbeer, San Francisco.
Cerebral Angiography in Intracranial Vascular Lesions, Homer G. McClintock, Denver.
Translumbar Aortography in Disease of the Aorta, Robert V. Elliott, Denver.
Uterosalpingography: Studies in Sterility, Thomas M. Fullenlove, San Francisco.

Guest speakers will participate at the luncheon sessions each day. A guest speakers' dinner (informal) Thursday, 6 p. m., will be followed by a joint meeting with the Denver Medical Society (Dr. Cyrus W. Anderson, Denver, president). Dr. Furey, who is president of the American College of Radiology, will serve as moderator for a session on roentgen film diagnoses with Drs. Meschan, Hope, Ralph C. Moore, Omaha, and John P. McGraw, Houston, Texas, as panelists. The Colorado Radiological Society will be host at the social hour following the scientific session. The banquet (strictly informal) is scheduled for Friday, 7:30 p. m., after a social hour. Dr. Popma will preside, and Dr. John S. Bouslog, Denver, will serve as toastmaster. Saturday will be devoted to a trip to Central City, with dinner at the Teller House, 6 p. m., and the play, "Bus Stop," at the Central City Opera House, 8:15 p. m.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States and its territories and possessions in the weeks ended as indicated:

Area	July 16, 1955: Paralytic Type	July 16, 1955: Total Cases Reported	July 17, 1954, Total
New England States			
Maine	1	1	1
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	35	52	9
Rhode Island	2	5	..
Connecticut	1	5	10
Middle Atlantic States			
New York	13	43	27
New Jersey	..	16	21
Pennsylvania	..	10	12
East North Central States			
Ohio	3	21	51
Indiana	2	7	10
Illinois	9	29	34
Michigan	9	31	54
Wisconsin	7	14	3
West North Central States			
Minnesota	1	2	6
Iowa	2	14	47
Missouri	2	10	17
North Dakota	..	4	3
South Dakota	..	..	6
Nebraska	7	8	33
Kansas	1	8	30
South Atlantic States			
Delaware	..	..	2
Maryland	1	2	6
District of Columbia	2	2	4
Virginia	3	8	13
West Virginia	1	1	6
North Carolina	2	20	13
South Carolina	3	15	21
Georgia	5	6	32
Florida	1	10	59
East South Central States			
Kentucky	4	10	25
Tennessee	3	9	24
Alabama	3	3	12
Mississippi	3	15	32
West South Central States			
Arkansas	6	11	13
Louisiana	1	3	37
Oklahoma	..	8	51
Texas	36	83	140
Mountain States			
Montana	..	..	..
Idaho	4	6	1
Wyoming	..	..	9
Colorado	2	2	7
New Mexico	2	4	9
Arizona	..	3	20
Utah	..	1	1
Nevada	..	2	2
Pacific States			
Washington	5	7	12
Oregon	4	5	6
California	18	49	122
Territories and Possessions			
Alaska	..	..	6
Hawaii	2	2	3
Puerto Rico	5	5	..
Total	211	572	1,062

Research in Mental Health.—The Ford Foundation has announced an extensive program of support for research in mental health. Programs eligible for such support will include: personality dynamics and development; biological, physiological, and somatic aspects of mental health; social and community aspects; studies in therapy; and children's disorders. The research programs may be located in any qualified institution in the U. S. or abroad. It is estimated that the programs will operate within the range of $50,000 to $150,000 a year and that the average will fall somewhat below $100,000 a year. The criteria to be used in selecting programs for support are: clear relevance for the field of mental health; specific nature and content of the program; past and potential quality of performance of personnel, with special attention to qualifications of the program's leadership; proper organizational arrangements within the institution; provision of research training in connection with the research program; integration of attack on the problem against other disciplines or research approaches, where appropriate; complementary relationship to other research programs in the same or related fields; and no displacement of existing funds. Applicants are asked to submit a full description of their proposed programs of research. Each application should be submitted in eight copies,

accompanied by an official letter of submission from the principal administrative officer of the sponsoring institution. Applicants who are unable to submit proposals by Sept. 1 but intend to do so later are asked to send a statement to that effect by that date to the Secretary, Ford Foundation, 477 Madison Ave., New York 22.

Postdoctoral Fellowships.—The award of a second group of postdoctoral fellowships during the current calendar year will be made by the National Science Foundation Oct. 20. Applications will be received through Sept. 12. The postdoctoral fellowships are awarded to U. S. citizens who will begin or continue their studies at the postdoctoral level in the life and physical sciences (including interdisciplinary fields) at any time within one year after the announcement of awards. Selection will be made solely on the basis of ability as shown in academic records, in written evaluation of each individual by faculty advisers or other qualified observers, and in a proposed plan of research. The stipend for National Science Foundation postdoctoral fellowships is $3,400 a year. Dependency allowances are made to all married fellows. A limited allowance to aid in defraying cost of travel will be paid as will tuition and certain fees collected from individuals of similar academic standing. Application materials may be obtained from the Fellowship Office, National Research Council, 2101 Constitution Ave., N. W., Washington 25, D. C.

FOREIGN

Congress on Anesthesiology.—The World Congress of Anesthesiologists will convene in the Kurhaus at Scheveningen near The Hague (Holland), Sept. 4-10. The subjects of the congress will be (1) the physiological, pharmacological, and clinical aspects of muscle relaxation, hypotension, hypothermia, and artificial hibernation, (2) respiration and circulation, and (3) the teaching of anesthesia.

Symposium on Migraine and Vascular Allergy.—At its second symposium in Basle, Switzerland, July 3-8, the Collegium Internationale Allergologicum had as its main theme "Migraine and Vascular Allergy." The presentations included "Migraine and Other Vascular Headaches" by Dr. Harold G. Wolff, New York, and "Food-Induced Allergic Headaches in Nonmigrainous and Migrainous Individuals" by Dr. William Kaufman, Bridgeport, Conn.

International Pharmaceutical Congress.—The 16th general assembly of the Fédération Internationale Pharmaceutique will convene in London, England, Sept. 19-23. Among the topics for discussion will be: Tests for the Sterility of Pharmaceutical Preparations; Absorption of Medicaments by Various Routes of Administration; Professional Liability and Professional Insurance Against Risks; and Pharmacy of Blood, Blood Products, and Blood Substitutes. The following symposiums have been scheduled: Standardization of Medicinal Plants; Determination of the Active Principles of Drugs and the Unification of Methods of Assay; and Recent Advances in Phytotherapy.

Neuropsychiatric Meetings.—The convention of the German Society of Neurologists and Psychiatrists will be held Sept. 19-22 at the University of Hamburg in Germany. The main subject is the "Motor Apparatus, Its Functions and Mode of Action." A group discussion on "The Training of the Neurologist" is scheduled. On Wednesday at 8 p. m. there will be a session of the Association of German Neurologists. Social events will include opera or the theater, dinner at the Hotel Atlantic, a steamship excursion to Helgoland, excursions through the fort of Hamburg, and visits to various museums. For information write to Dr. Magun, Nervenklinik, Hamburg-Eppendorf, Germany.

Congress on Hematology.—The fifth International Congress of the European Society of Hematologists, organized in cooperation with the German Hematological Society, will be held in Freiburg im Breisgau, Western Germany, Sept. 20-25. Sessions are open to all physicians and scientists interested in hematology. Topics for discussion include: isotopes and cytostatics in hematology; metabolism of iron and copper; neurohumoral regulation of the blood; hepatolienal diseases and their relations to hematology; the heredity of the hemorrhagic diathesis; anticoagulant therapy and prophylaxis of the arterial thrombosis; and hematopoiesis and bone structure. On Sunday there will be a common session on "Biochemistry of the Antibodies" with the Societé Internationale de Transfusion Sanguine and the Deutschen Gesellschaft für Bluttransfusionen.

CORRECTION

Urologic Complications of Sickle Cell Disease.—Line 22 in the abstract on sickle cell disease on page 551 of the issue of Feb. 5, 1955, should read: "hormone plays a causal role in the priapism of sickle cell disease," not "a causal role in sickle cell disease."

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secretary.

1955 Clinical Meeting, Boston, Nov. 29-Dec. 2.

1956 Annual Meeting, Chicago, June 11-15.

1956 Clinical Meeting, Seattle, Nov. 27-30.

1957 Annual Meeting, New York, June 3-7.

AMERICAN MEDICAL ASSOCIATION PUBLIC RELATIONS INSTITUTE, Drake Hotel, Chicago, Aug. 31- Sept. 1. Mr. Leo E. Brown, 535 N. Dearborn St., Chicago 10, Director.

AMERICAN ASSOCIATION OF NURSING HOMES, Hotel Muehlebach, Kansas City, Mo., Sept. 19-21. Mr. Ira O. Wallace, P.O. Box 366, New Castle, Ky., Secretary.

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS, The Homestead, Hot Springs, Va., Sept. 8-10. Dr. Frank R. Lock, Bowman Gray School of Medicine, Winston-Salem, N. C., Secretary.

AMERICAN COLLEGE OF HOSPITAL ADMINISTRATORS, Convention Hall, Atlantic City, N. J., Sept. 17-19. Mr. Dean Conley, 620 North Michigan Ave., Chicago 11, Executive Director.

AMERICAN CONGRESS OF PHYSICIAL MEDICINE AND REHABILITATION, Hotel Statler, Detroit, Aug. 28-Sept. 2. Dr. Frances Baker, 30 North Michigan Ave., Chicago 2, Secretary.

AMERICAN FRACTURE ASSOCIATION, Hotel Fontainebleau, Miami Beach, Fla., Sept. 19-22. Dr. Homer D. Junkin, Paris Hospital, Paris, Ill., Secretary.

AMERICAN HOSPITAL ASSOCIATION, Traymore Hotel, Atlantic City, N. J., Sept. 19-22. Dr. Edwin L. Crosby, 18 East Division St., Chicago 10, Director.

AMERICAN MEDICAL WRITERS' ASSOCIATION, Jefferson Hotel, St. Louis, Sept. 30-Oct. 1. Dr. Harold Swanberg, P.O. Drawer 110, Quincy, Ill., Secretary.

AMERICAN PHYSIOLOGICAL SOCIETY FALL MEETING, Tufts College, Medford, Mass., Sept. 6-9. Dr. Allan C. Burton, Univ. of Western Ontario, London, Ont., Canada, Secretary.

AMERICAN ROENTGEN RAY SOCIETY, Palmer House, Chicago, Sept. 20-23. Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Secretary.

AMERICAN SOCIETY OF PLASTIC AND RECONSTRUCTIVE SURGERY, Atlantic City, N. J., Sept. 25-30. Dr. Kenneth L. Pickrell, Duke Hospital Durham, N. C., Secretary.

AMERICAN VETERINARY MEDICAL ASSOCIATION, Radisson Hotel and Auditorium, Minneapolis, Aug. 15-18. Dr. J. G. Hardenbergh, 600 South Michigan Blvd., Chicago 5, Executive Secretary.

BIOLOGICAL PHOTOGRAPHIC ASSOCIATION, Wisconsin Hotel, Milwaukee, Aug. 30-Sept. 2. Miss June H. Waters, c/o Pavelle Color, Inc., 533 W. 57th St., New York 19, Executive Secretary.

CLINICAL ORTHOPAEDIC SOCIETY, Skirvin Hotel, Oklahoma City, Sept. 30-Oct. 1. Dr. Marcus J. Stewart, 869 Madison Ave., Memphis, Tenn., Executive Secretary.

COLORADO STATE MEDICAL SOCIETY, Shirley-Savoy Hotel, Denver, Sept. 20-23. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary.

INDUSTRIAL HEALTH CONFERENCE, Shamrock Hotel, Houston, Texas, Sept. 22-23. Dr. Sidney Schnur, 411 Medical Arts Bldg., Houston 2, Texas, Chairman.

KENTUCKY STATE MEDICAL ASSOCIATION, Louisville, Sept. 27-29. Mr. J. P. Sanford, 620 S. Third St., Louisville, Executive Secretary.

MICHIGAN STATE MEDICAL SOCIETY, Pantlind Hotel, Grand Rapids, Sept. 26-30. Dr. L. Fernald Foster, 606 Townsend St., Lansing 5, Secretary.

MISSISSIPPI VALLEY MEDICAL SOCIETY, Jefferson Hotel, St. Louis, Sept. 28-30. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

MONTANA MEDICAL ASSOCIATION, Baxter Hotel, Bozeman, Sept. 15-18. Mr. L. R. Hegland, P.O. Box 1692, Billings, Executive Secretary.

NATIONAL MEDICAL ASSOCIATION, Los Angeles, Aug. 8-11. Dr. John T. Givens, 1108 Church St., Norfolk 10, Va., General Secretary.

NEVADA STATE MEDICAL ASSOCIATION, Riverside Hotel, Reno, Aug. 18-20. Dr. William A. O'Brien III, 505 Chestnut St., Reno, Secretary.

NEW ENGLAND HEALTH INSTITUTE, Colby College, Waterville, Me., Aug. 30-Sept. 1. Dr. Edward W. Colby, City of Portland Health Dept., Portland, Me., Chairman.

NEW HAMPSHIRE MEDICAL SOCIETY, Mt. Washington Hotel, Bretton Woods, Sept. 29-Oct. 1. Dr. Warren H. Butterfield, 18 School St., Concord, Secretary.

NORTH TEXAS-SOUTHERN OKLAHOMA FALL CLINICAL CONFERENCE, Wichita Falls, Tex., Sept. 17. Dr. E. C. Bebb, Broad St., Wichita Falls, Tex., Chairman.

OREGON STATE MEDICAL SOCIETY, Hotel Heathman, Portland, Sept. 28-Oct. 1. Dr. Richard R. Carter, 1020 S.W. Taylor St., Portland 5, Secretary.

PACIFIC DERMATOLOGIC ASSOCIATION, Mexico, D. F., Mexico, Aug. 22-24. Dr. Ben A. Newman, 436 N. Roxbury Drive, Beverly Hills, Calif., Secretary.

PENNSYLVANIA, MEDICAL SOCIETY OF THE STATE OF, William Penn Hotel, Pittsburgh, Sept. 18-23. Dr. Harold B. Gardner, 230 State St., Harrisburg, Secretary.

POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY AND METABOLISM, Indianapolis, Sept. 26-Oct. 1. Dr. John J. Mahoney, Assistant Dean, Indiana University School of Medicine, 1040 W. Michigan St., Indianapolis 7.

REGIONAL MEETINGS, AMERICAN COLLEGE OF PHYSICIANS:
Jamestown, N. D., Sept. 10. Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Executive Secretary.

RENO SURGICAL SOCIETY, Reno, Nev., Aug. 18-20. Dr. James R. Herz, 509 Humboldt St., Reno, Nev., Secretary.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY, Shirley-Savoy Hotel, Denver, Aug. 18-20. Dr. John H. Freed, 4200 East 9th St., Denver 20, Secretary.

SOCIETY OF GENERAL PHYSIOLOGISTS, Marine Biological Laboratory, Woods Hole, Mass., Sept. 9-10. Dr. A. M. Shanes, National Institutes of Health, Bethesda 14, Md.

SOUTHWESTERN SURGICAL CONGRESS, Muehlebach Hotel, Kansas City, Mo., Sept. 5-7. Dr. C. M. O'Leary, 207 Plaza Court Bldg., Oklahoma City, Secretary.

U. S. CHAPTER, INTERNATIONAL COLLEGE OF SURGEONS, Convention Hall, Philadelphia, Sept. 12-15. Dr. Karl Meyer, 1516 Lake Shore Drive, Chicago 10, Secretary.

UTAH STATE MEDICAL ASSOCIATION, Union Bldg., Salt Lake City, Sept. 8-10. Mr. H. Bowman, 42 S. Fifth East St., Salt Lake City 2, Executive Secretary.

VERMONT STATE MEDICAL SOCIETY, Mt. Washington Hotel, Bretton Woods, N. H., Sept. 28-Oct. 1. Dr. James P. Hammond, 337 South St., Bennington, Secretary.

WASHINGTON STATE MEDICAL ASSOCIATION, Olympic Hotel, Seattle, Sept. 11-14. Dr. Frederick A. Tucker, 1309 Seventh Ave., Seattle 1, Secretary.

WESTERN ASSOCIATION OF RAILWAY SURGEONS, Las Vegas, Nev., Sept. 22-24. Dr. Leo L. Stanley, 1322 Fifth Ave., San Rafael, Calif., Secretary.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, White Sulphur Springs, Aug. 18-20. Mr. Charles Lively, P. O. Box 1031, Charleston 24, Executive Secretary.

FOREIGN AND INTERNATIONAL

AUSTRALASIAN MEDICAL CONGRESS, Sydney, N.S.W., Australia, Aug. 20-27. For information write: Federal Council of the B.M.A. in Australia, 135 Macquaire St., Syndey, N.S.W., Australia.

CANADIAN SOCIETY FOR THE STUDY OF FERTILITY, Royal York Hotel, Toronto, Ont., Canada, Oct. 6-8. Dr. Earl R. Plunkett, 469 Waterloo St., London, Ont., Canada, Secretary.

CONGRESS OF INTERNATIONAL ASSOCIATION OF LIMNOLOGY, Helsinki, Finland, July 26-Aug. 7, 1956. For information address: Dr. H. Luther, Snellmansgatan 16 C 36, Helsinki, Finland.

CONGRESS OF INTERNATIONAL SOCIETY FOR RESEARCH ON ANESTHESIA, Miami Beach, Fla., U.S.A., Mar. 12-15, 1956. For information write: Dr. R. J. Whitacre, 13951 Terrace Road, Cleveland 12, Ohio, U. S. A.

CONGRESS OF INTERNATIONAL UNION OF RAILWAY MEDICAL SERVICES, Dubrovnik, Yugoslavia, Sept. 19-24. Dr. Jovanovic, Head Office, Yugoslav Railway, Belgrade, Yugoslavia, President.

CONGRESS OF INTERNATIONAL UNION AGAINST VENEREAL DISEASES, Naples, Italy, Sept. 25-28. For information address: Prof. Monacelli, University of Naples, Dept. of Dermatology, Naples, Italy.

INTERNATIONAL ACADEMY OF LEGAL AND SOCIAL MEDICINE, Plenary Conference, Genes, Italy, Oct. 13-17. Prof. Domenico Macaggi, Institut de Medicine legale, Universite de Genes, Genes, Italy, President.

INTERNATIONAL CONFERENCE OF MEDICAL LIBRARIANS AND REFERENCE LIBRARIANS, University Hall, Brussels, Belgium, Sept. 10. For information address: Miss Ch. de Looze, Librarian % Oeuvre Nationale Belge de Defense contra la Tuberculose, 56, rue de la Concorde, Brussels, Belgium.

INTERNATIONAL CONFERENCE ON RADIOBIOLOGY, Cambridge, England, Aug. 14-17. For information write: Dr. Barbara E. Holmes, Dept. of Radiotherapeutics, Univ. of Cambridge, Downing St., Cambridge, England.

INTERNATIONAL CONGRESS OF ALLERGOLOGY, Rio de Janeiro, Brazil, S. A., Nov. 6-13. Dr. Bernard N. Halpern, 197 boulevard St. Germain, Paris 7e, France, Secretary General.

INTERNATIONAL CONGRESS OF ANGIOLOGY AND HISTOPATHOLOGY, Fribourg, Switzerland, Sept. 2-5. For information write: Dr. Gerson, 4 rue Pasquier, Paris 8e, France.

INTERNATIONAL CONGRESS OF CRIMINOLOGY, London, England, Sept. 11-18. For information write: Dr. Carroll, 28 Weymouth St., London, W.1, England.

INTERNATIONAL CONGRESS OF EUROPEAN SOCIETY OF HAEMATOLOGY, Freiburg i,Br., Germany, Sept. 20-24. Prof. Dr. L. Heilmeyer, Hugstetter Strasse 55, Freiburg i,Br., Germany, Chairman.

INTERNATIONAL CONGRESS OF INTERNATIONAL COLLEGE OF SURGEONS, Buenos Aires, Argentina, S. A., Nov. 19-24, 1956. Dr. Max Thorek, 1516 Lake Shore Drive, Chicago, Illinois, U. S. A., Secretary-General.

INTERNATIONAL CONGRESS OF INTERNATIONAL SOCIETY OF BRONCHOESOPHAGOLOGY, Buenos Aires, Argentina, S. A., Oct. 28-29. Dr. Juan Carlos Arauz, Cangallo 4015, Buenos Aires, Argentina, S. A., Secretary General.

INTERNATIONAL CONGRESS OF LIBRARIANSHIP AND DOCUMENTATION, Brussels, Belgium, Sept. 11-18. For information write: Dr. A. C. Breycha-Vauthier, Librarian, United Nations, Geneva, Switzerland.

INTERNATIONAL CONGRESS OF MEDICAL PROFESSIONAL JURISDICTION, MEDICAL ETHICS, AND COMPARATIVE MEDICAL LAW, Paris, France, Sept. 30-Oct. 3. Dr. J. R. DeBray, Conseil National de L'Ordre des Medécins, 60, Boulevard Latour-Maubourg, Paris 7e, France, Secretary General.

INTERNATIONAL CONGRESS OF MILITARY MEDICINE AND PHARMACY, Istanbul, Turkey, Aug. 28-Sept. 1. Dr. J. Voncken, International Committee of Military Medicine and Pharmacy, 79 rue Saint Laurent, Liege, Belgium, Secretary-General.

INTERNATIONAL CONGRESS OF NEO-HIPPOCRATIC MEDICINE, Montecatini, Terme, Italy, May 20-22, 1956. Prof. P. Delore, 13 rue Jarente, Lyon, France, Secretary-General.

INTERNATIONAL CONGRESS OF NEUROPATHOLOGY, London, England, Sept. 12-17. Dr. W. H. McMenemey, Maida Vale Hospital for Nervous Diseases, London, W.9, England, Secretary.

INTERNATIONAL CONGRESS OF PAEDIATRICS, Copenhagen, Denmark, July 22-27, 1956. Professor P. Plum, Rigshospitalet, Copenhagen, Denmark, President.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, Copenhagen, Denmark, August 20-24, 1956. Dr. B. Strandberg, Kobenhavns amts sygehus i Gentofte, Dept. of Rheumatology and Physical Medicine, Hellerup, Denmark, Honorable Secretary.

INTERNATIONAL CONGRESS OF RADIOLOGY, Mexico, D. F., Mexico, July 22-28, 1956. Dr. Jose Noriega, Tepic 126 (2e piso), Mexico, D. F. 7, Mexico, Secretary General.

INTERNATIONAL CONGRESS ON URINARY LITHIASIS, Evian, France, Sept. 2-4. Mr. Rossollin-Grandville, Direction Cachet, Evian (Hte-Savoie), France, Secretary General.

INTERNATIONAL CONGRESS OF WORLD CONFEDERATION FOR PHYSICAL THERAPY, New York, New York, U. S. A., June 17-23, 1956. For information address: Miss Mildred Elson, American Physical Therapy Association, 1790 Broadway, New York 19, New York, U. S. A.

INTERNATIONAL GENERAL MEDICAL CONGRESS, University of Rosario Medical College, Rosario, Argentina, S. A., Nov. 7-12. Dean Jose Imhoff, Santa Fé 3100, Rosario, Argentina, S. A., Chairman.

INTERNATIONAL MEDICAL CONGRESS, Verona, Italy, Sept. 1-4. For information write: c/o Offices of the International Verona Fair, Piazza Bra., Verona, Italy.

INTERNATIONAL OFFICE OF DOCUMENTATION OF MILITARY MEDICINE, Istanbul, Turkey, Aug. 28-Sept. 1. Dr. J. Voncken, 79 rue Saint Laurent, Liege, Belgium, Secretary-General.

INTERNATIONAL PHYSIOLOGICAL CONGRESS, Brussels, Belgium, July 29-Aug. 5, 1956. For information address: Prof. J. Reuse, Faculte de Medicine et de Pharmacie, 115 Boulevard de Waterloo, Brussels, Belgium.

INTERNATIONAL SOCIETY FOR THE STUDY OF BIOLOGICAL RHYTHMS, Stockholm, Sweden, Sept. 15-17. For information write: Prof. Ture Petrén, Karolinska Institutet, Stockholm 60, Sweden.

INTERNATIONAL VITAMIN E CONGRESS, Cini Foundation, Island of San Giorgio Maggiore, Venice, Italy, Sept. 5-8. Prof. Emilio Raverdino, via Pietro Verri 4, Milano, Italy, Secretary.

NEURORADIOLOGIC SYMPOSIUM, London, England, Sept. 13-17. Dr. R. D. Hoare, National Hospital, Queen Square, London, W.C.1, England, Secretary.

PAN AMERICAN CONGRESS OF INTERNATIONAL COLLEGE OF SURGEONS, Mendoza City, Argentina, S. A., Oct. 22-26. For information address: Secretary, Caseros Av. 2154, Buenos Aires, Argentina, S. A.

PAN AMERICAN CONGRESS OF OPHTHALMOLOGY, Santiago, Chile, S. A., Jan. 9-14, 1956. Dr. Rene Contardo, Huerfanos 930, Of. 74, Santiago, Chile, Secretary General.

PAN AMERICAN CONGRESS ON RHEUMATIC DISEASES, Rio de Janeiro and Sao Paulo, Brazil, S. A., Aug. 14-20. For information write: Dr. Waldemar Bianchi, 126 Avenida Franklin D. Roosevelt, Rio de Janeiro, Brazil, S. A.

PAN AMERICAN MEDICAL WOMEN'S ALLIANCE, Santiago, Chile, Mar. 6-13, 1956. For information address: Dr. Eva Cutright, 458 Beall Ave., Wooster, Ohio, U. S. A.

PAN AMERICAN MEDICAL SOCIAL CONVENTION, Bogota, Colombia, S. A., Oct. 15-22. Dr. Leopoldo E. Araujo, Avenida de los Presidentes Num. 506, Apartado 2589, La Habana, Cuba, Secretary.

VENEZUELAN CONGRESS OF MEDICAL SCIENCES, Caracas, Venezuela, S. A., Nov. 18-26. Dr. A. L. Briceno Rossi, Apartado 4412, Ofic. del Este, Caracas, Venezuela, S. A., Secretary General.

WORLD CONGRESS OF ANESTHESIOLOGISTS, Scheveningen, Netherlands, Sept. 5-10. For information write: Mr. W. A. Fentener van Vlissingen, Noordt-Houdringelaan, 24, Bilthoven, Netherlands.

WORLD CONGRESS ON FERTILITY AND STERILITY, Naples, Italy, May 18-26, 1956. For information address: Prof. G. Tesauro, S. Andrea della Dame, 19, Naples, Italy.

WORLD CONGRESS OF JEWISH PHYSICIANS, Haifa, Tel-Aviv, Jerusalem, Israel, Aug. 10-17. Dr. Z. Avigdori, P.O.B. 1342, Jerusalem, Israel, Chairman.

WORLD FEDERATION FOR MENTAL HEALTH, Istanbul, Turkey, Aug. 21. For information write: Miss E. M. Thornton, 19 Manchester St., London, W.1, England.

WORLD MEDICAL ASSOCIATION, Vienna, Austria, Sept. 20-26. Dr. Louis H. Bauer, 345 East 46th St., New York 17, N. Y., U. S. A., Secretary General.

EXAMINATIONS AND LICENSURE

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Part I*, Sept. 6-7. Candidates may file applications at any time, but the National Board must receive them at least six weeks before the date of the examination. New candidates should apply by formal registration; registered candidates should notify the board by letter and forward their fees. Exec. Sec., Dr. John B. Hubbard, 133 South 36th St., Philadelphia 4.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Oral*. New York City, Oct. 23-27. Sec., Dr. Curtiss B. Hickcox, 80 Seymour St., Hartford 15.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: *Oral*. Washington, D. C., Oct. 14-16. Final date for filing application was March 15. Sec., Dr. B. M. Kesten, One Haven Ave., New York 32, N. Y.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral*. Portland, Ore., Sept. 14-16; Chicago, Nov. 30-Dec. 1. *Subspecialties. Cardiovascular Disease*. Chicago, Nov. 30. The closing date for acceptance of applications for gastroenterology was Feb. 1, and for cardiovascular disease the closing date was June 1. Exec. Sec., Dr. William A. Werrell, 1 West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral*. New Haven, November. Oral examinations given in Spring and Fall. Final date for filing application for the Spring examination is October 1; for the Fall examination April 1. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Applications for certification for the 1956 Part I examinations are now being accepted. Final date for filing application is Oct. 1. Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Practical Examination*. Chicago, Oct. 9-14. Final date for filing application for 1955 practical examination was July 1, 1954. *Written*. January, 1956. Final date for filing application was July 1. *Practical Examination*. St. Louis, Oct. 20-25. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: Final date for filing application for the Part II examination to be given in January 1956 is Aug 15. Sec., Dr. Harold A. Sofield, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral*. Chicago, Oct. 3-7. Final date for filing application is April. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PEDIATRICS: *Oral*. Chicago, Oct. 7-9; and Washington, D. C., Dec. 2-4. Admin. Sec., Mrs. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PLASTIC SURGERY: *Oral and Written*. Philadelphia, Sept. 22-24. Corres. Sec., Miss Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Certification in Public Health*. Kansas City, Mo., Nov. 10-12. Sec.-Treas., Dr. Ernest L. Stebbins, 615 N. Wolfe St., Baltimore 5.

AMERICAN BOARD OF PROCTOLOGY: *Part II*. Philadelphia, Sept. 17. Sec., Dr. Stuart T. Ross, 131 Fulton Ave., Hempstead, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: San Francisco, mid-October; New York City, December. Sec., Dr. David A. Boyd, 102-110 Second Ave. S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Chicago, Dec. 4. Final date for filing applications for the fall examination was July 1. Candidates who will complete their training by Dec. 31 will be eligible to appear for this examination. Sec., Dr. B. R. Kirklin, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Part I*. Centers throughout the United States, in Europe and in the Far East, Oct. 26 and March 28. Closing date for the October examination was July 1 and for the March examination is December 1. *Part II*. Buffalo, Sept. 26-27; Chicago, Oct. 27-28; New York City, Nov. 14-15; St. Louis, Dec. 12-13; New Orleans, Jan. 16-17; Los Angeles, Feb. 13-14; San Francisco, Feb. 16-17; Durham, Mar. 12-13; Boston, May 14-15 and Philadelphia, June 4-5. Sec., Dr. John B. Flick, 255 S. Fifteenth St., Philadelphia 2.

THE BOARD OF THORACIC SURGERY: *Written*. Various Centers, Sept. 9. Final date for filing applications was July 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

MAGAZINE–TELEVISION REPORT

The following list of current medical articles in mass-circulation magazines and forthcoming network television programs on medical subjects is published each week only for the information of readers of THE JOURNAL. *Unless specifically stated, the American Medical Association neither approves nor disapproves of the articles and programs reported.*

TELEVISION

Monday, August 8

NBC-TV, 9 p. m. EDT. "Medic" presents "The Wild Intruder," a rerun of a story about a young woman who gains courage for a new life after an operation for breast cancer.

Tuesday, August 9

CBS-TV, 10:30 p. m. EDT. "The Search" repeats a program from last season. Filmed at New York University-Bellevue Medical Center, it is titled "Independence for Paraplegics."

MAGAZINES

Ladies' Home Journal, August, 1955

"Babies Should Be Born at Home!" by Dr. M. F. Ashley Montagu

The author presents arguments in favor of having children at home and says: "The family is a unit, and its unity should never be broken. If that unity must be disturbed, it should never be in the manner so mechanically and unnecessarily produced by the usual obstetrical hospital."

Cosmopolitan, August, 1955

"A New Drug Brings Relief for the Tense and Anxious," by Lawrence Galton

"A new drug, Miltown . . . promises quick and safe relief for the tense and anxious. . . . Miltown is the most recent derivative of mephenesin. Not only is it effective, it is also free of penalty. The usual dose is one 400-milligram tablet after each meal and one at bedtime."

Family Weekly Magazine, July 31, 1955

"What's Behind Your Headaches?" by Regina Gruss

"This common complaint is a symptom, not a disease; it may be the harbinger of serious trouble." The article concludes with this advice: "Your general practitioner is well-equipped to tackle the problem. You can help him and yourself by seeing him promptly and cooperating with him fully."

Harper's Magazine, August, 1955

"The Salk Vaccine: What Caused the Mess?" by Leonard Engel

In analyzing what is called "the chaotic confusion over the polio inoculations," the author placed primary blame on governmental agencies. He says, "The Health Service and the Department (of Health, Education and Welfare) not only hurt the polio program and themselves by doing the wrong things. They did it through plainly avoidable public-relations ineptness." In two places Mr. Engel scolds the American Medical Association, together with the National Foundation for Infantile Paralysis and the Public Health Service, for failing to inform the public that vaccine takes some time to produce immunity and for the "notable lack of real planning for the technical aspects of producing vaccine."

Look, August 9, 1955

"Hiroshima Diary," by Dr. Michihiko Hachiya

An account of the Hiroshima atomic bombing through the eyes of a Japanese physician.

Saturday Evening Post, July 30, 1955

"They Heal Heartsick Children," by Jerome Ellison

The story of a nonprofessional volunteer organization called Recreation Service, Children of Bellevue, Inc. Dr. Randolph A. Wyman, Bellevue's medical superintendent, is quoted in the article as saying, "These amateurs are regarded as indispensable members of the hospital staff. We could no more do without them than we could do without penicillin."

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DEATHS

Terry, Benjamin Taylor ✙ Rochester, Minn.; born in Birmingham, Ala., June 10, 1876; Johns Hopkins University School of Medicine, Baltimore, 1904; research fellow in pathology at the University of Chicago, 1904 to 1905; member of the staff of the Rockefeller Institute for Medical Research in New York City from 1906 to 1913; director of laboratories at the Kings County Hospital in Brooklyn from 1913 to 1918; instructor of pathology at Columbia University College of Physicians and Surgeons in New York City from 1914 to 1918; professor of pathology at the Vanderbilt University School of Medicine and pathologist at the Vanderbilt University Hospital in Nashville, Tenn., from 1918 to 1925; postgraduate instructor in pathology at the University of North Carolina in the summer of 1923; director of laboratories at the Toledo (Ohio) General Hospital, 1925 to 1926; from 1926 to 1932 was at the Mayo Clinic as research worker on malignancy; acting professor of pathology at the University of Texas School of Medicine in Galveston, 1932 to 1933; for many years on the staff of the Tacoma (Wash.) General Hospital; specialist certified by the American Board of Pathology; member of the American Association for the Advancement of Science and the American Society of Clinical Pathologists, which in 1938 awarded him its gold medal for an exhibit on "Aids in Rapid Diagnosis of Tissues"; emeritus member of the College of American Pathologists; the American Medical Association in 1923 awarded him a Silver medal "for the demonstration of instructive specimens of pathologic anatomy," in 1924 the Bronze medal, in 1927 a Certificate of Merit "for exhibit of new stain and method of tissue microscopy and excellence of demonstration," in 1928 special mention "for excellence of personal demonstration," and in 1947 honorable mention "for exhibit on Razor Section Technic and the Polychroming of Methylene Blue"; from 1911 to 1913 joint editor of *Journal of Experimental Medicine;* died June 14, aged 78.

Camp, Carl Dudley ✙ Ann Arbor, Mich.; born in South Watauga, Tenn., Oct. 2, 1880; University of Pennsylvania Department of Medicine, Philadelphia, 1902; interned at the Howard Hospital in Philadelphia; from 1904 to 1907 instructor in neurology and neuropathology at his alma mater and assistant neurologist at Philadelphia General, Philadelphia Polyclinic, and University of Pennsylvania hospitals; in 1907 joined the faculty of the University of Michigan Medical School as clinical professor of diseases of the nervous system; in 1920 his title was changed to that of professor of neurology; later became professor emeritus of neurology; member of the American Neurological Association, of which he was formerly vice-president; one of the original members of the Central Neuropsychiatric Association; in 1914 president of the Detroit Neurological Society (now the Michigan Society of Neurology and Psychiatry); member of the Philadelphia Neurological Society, American Association of Pathologists and Bacteriologists, the American Psychopathological Association, the Research Club of the University of Michigan, Nu Sigma Nu, Alpha Omega Alpha, and Sigma Xi; honorary member of the American Academy of Neurology; died in the University Hospital May 23, aged 74, of hemorrhage from the urinary bladder.

Mandelbaum, Harry ✙ Brooklyn, N. Y.; born in New York City March 10, 1895; Long Island College Hospital, Brooklyn, 1919; on the faculty of State University College of Medicine at New York City; fellow of the American College of Physicians, American College of Cardiology, American College of Chest Physicians, American Geriatrics Society, and the New York Academy of Medicine; member of the board of trustees and past-treasurer of the Medical Society of the County of Kings; fellow and secretary of the Brooklyn Society of Internal Medicine; member of the executive board of the New York Cardiological Society, of which he was a fellow; member of the World Medical Association; specialist certified by the American Board of Internal Medicine; physician in charge of the hypertension and nephritis clinic at the Jewish Hospital of Brooklyn, where he was associate in medicine; attending in medicine at the Jewish Sanitarium and Hospital for Chronic Diseases and the Brooklyn Hebrew Home and Hospital for the Aged; joint author with Dr. William Dock of "Ballistocardiography"; died May 27, aged 60, of coronary occlusion with infarction.

Kramer, Gabriel Bernard ✙ Washington, D. C.; born in Russia April 1, 1884; Baltimore Medical College, 1907; also a lawyer; specialist certified by the American Board of Pathology; fellow of the American College of Physicians; founding fellow of the College of American Pathologists; member of the American Society of Clinical Pathologists; deputy coroner of Ramsay County in St. Paul from 1919 to 1923; from 1909 to 1913 instructor of anatomy at Flint Medical College of New Orleans University; associate professor of pathology at the New York Medical and Flower Hospital in New York City from 1944 to 1946; from 1916 to 1923 pathologist and director of laboratories at Ancker Hospital in St. Paul, and the Youngstown (Ohio) Hospital from 1923 to 1945; formerly consulting pathologist at the Salem (Ohio) City Hospital and the New Castle (Pa.) Hospital; for many years pathologist and director of laboratories at the Swedish-American Hospital in Rockford, Ill.; died in the Georgetown University Hospital April 6, aged 73, of cerebral hemorrhage.

Ellis, Bert Edward ✙ Indianapolis; born in Linton, Ind., Nov. 23, 1889; Indiana University School of Medicine, Indianapolis, 1921; clinical professor of otorhinolaryngology at his alma mater, where he held various positions on the faculty; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Oto-Laryngology and the American Laryngological, Rhinological and Otological Society; past-president of the Indianapolis Medical Society, serving on its council for three years, and in 1948 acting chairman of the council; member of the board of directors of the American Otorhinologic Society for Plastic Surgery, of which he was president and vice-president; on the staff of the Methodist, St. Vincent's, and Indianapolis General hospitals; during World War I served in the medical division of the student military training courses at his alma mater; active member of the otolaryngology section, St. Vincent's Hospital, where he died June 3, aged 65, of multiple myeloma.

Green, Robert Montraville ✙ Brookline, Mass.; born in Boston July 11, 1880; Harvard Medical School, Boston, 1906; continued training in Boston on the south surgical service at the Massachusetts General Hospital and subsequently served as intern at the Children's Hospital and at the Boston Lying-In Hospital; in 1930 became surgeon-in-chief of gynecology and obstetrics at the Boston City Hospital, a position he held until July, 1942; became an associate professor of applied anatomy at his alma mater, retiring as emeritus in 1947; member of the New England Obstetrical and Gynecological Society; in 1906 joined the staff of the *Boston Medical and Surgical Journal,* now the *New England Journal of Medicine,* as an assistant editor; in 1915 became editor-in-chief and continued in this position until 1921; remained on the editorial board since 1931; author of "A Translation of Galen's Hygiene (De Sanitate Tuenda)"; died May 29, aged 74, of acute myocardial infarction.

Nelson, Walter Garnett ✙ Medical Director, U. S. Public Health Service, Balboa Heights, Canal Zone; born in Washington, D. C., Aug. 28, 1895; Georgetown University School of Medicine, Washington, D. C., 1918; joined the U. S. Public Health Service in 1920; during World War II was district medical officer for the third Naval District in New York; was in quarantine activities in Germany, The Netherlands, and Italy; from 1950 until 1952 was in charge of quarantine and immigration activities in continental Europe, stationed in Paris; since 1952 on detail with the U. S. Quarantine Station; died May 18, aged 59, of coronary disease.

✙ Indicates Member of the American Medical Association.

Brown, Thomas Donald, Portsmouth, R. I.; Georgetown University School of Medicine, Washington, D. C., 1952; interned at the Gallinger Municipal Hospital in Washington, D. C.; served a residency at the Newport (R. I.) Hospital; also a graduate in pharmacy; certified by the National Board of Medical Examiners; member of the Rhode Island Medical Society; died in Newport May 2, aged 43, of cerebral embolism and aortic stenosis.

Browning, Albert Washington, Fluvanna, Texas; Chattanooga (Tenn.) Medical College, 1902; died in Snyder March 30, aged 78, of cerebral hemorrhage.

Brunson, Asa, El Paso, Texas; Memphis (Tenn.) Hospital Medical College, 1899; served during World War I; died June 15, aged 83.

Burress, Bert Overton, Washington, Ind.; Illinois Medical College, Chicago, 1905; member of the Indiana State Medical Association; served as city and county health officer; member of the city board of health; bank president; died in the Daviess County Hospital May 9, aged 77, of cerebral hemorrhage.

Caldwell, Austin Greene, Sinai, Ky.; Louisville (Ky.) Medical College, 1893; died in Lawrenceburg April 13, aged 88.

Callahan, Bernard Joseph, Denver; Jefferson Medical College of Philadelphia, 1900; died in the Veterans Administration Hospital in Cheyenne, Wyo., April 5, aged 89, of coronary thrombosis.

Clark, John D. ✠ Wichita, Kan.; Northwestern University Medical School, Chicago, 1901; past-president of the Sedgwick County Medical Society; charter member of the Central Association of Obstetrics and Gynecology; fellow of the American College of Surgeons; on the staffs of Wesley and Wichita hospitals and St. Francis Hospital, where he died June 6, aged 80, of cerebral thrombosis.

Clark, Vinton John ✠ Salt Lake City; Rush Medical College, Chicago, 1915; past-president of the Salt Lake County Medical Society and the Utah State Medical Association; formerly on the staff of St. Mark's Hospital; died June 12, aged 78.

Clarke, Harry Downer ✠ Seward, Neb.; John A. Creighton Medical College, Omaha, 1912; served during World War II; past-president of the Seward County Medical Society; died in Rochester, Minn., June 13, aged 69, of coronary insufficiency and hypertension.

Costner, George Henry, Lincolnton, N. C.; University of Maryland School of Medicine, Baltimore, 1901; died in the Gordon Crowell Memorial Hospital April 17, aged 76, of carcinoma of the urinary bladder.

Danielson, Wilford Aldrich ✠ Chicago; Chicago College of Medicine and Surgery, 1915; served during World War I; died June 29, aged 64, of cerebral hemorrhage, hypertension, and cancer of the prostate.

Davis, Charles Edward ✠ Dallas, Texas; University of Michigan Medical School, Ann Arbor, 1949; interned at the Hermann Hospital; formerly a resident at the Brackenridge Hospital in Austin; resident at the Parkland Hospital; served in the Korean War; died in Austin June 4, aged 29.

Denchfield, Arthur Leighton, Oradell, N. J.; University and Bellevue Hospital Medical College, New York City, 1905; assistant physician at Bergen Pines County Hospital in Paramus, where he died May 13, aged 74, of carcinoma.

Dickinson, Harry Barham ✠ Coulterville, Ill.; Washington University School of Medicine, St. Louis, 1927; served during World War I; company physician for the Illinois Central Railroad; on the staff of the Pinckneyville (Ill.) Hospital and St. Elizabeth's Hospital, Belleville, where he died June 11, aged 58, of retroperitoneal neurosarcoma.

Donais, Joseph Eusebe ✠ Southbridge, Mass.; School of Medicine and Surgery of Montreal, Canada, 1907; served on the board of health; died in St. Vincent Hospital, Worcester, May 17, aged 78, of carcinoma of the stomach.

Donaldson, Buck, Castor, La.; University of Alabama School of Medicine, Mobile, 1910; died May 5, aged 76, of cancer.

Donaldson, Frederick August ✠ Westwood, Mass.; Harvard Medical School, Boston, 1904; died May 5, aged 86, of arteriosclerotic heart disease.

Douglass, William Tyler ✠ Harrisburg, Pa.; Jefferson Medical College of Philadelphia, 1901; an associate member of the American Medical Association; fellow of the American College of Surgeons; past-president of the Harrisburg Academy of Medicine and the Dauphin County Medical Society; served on the staff of Harrisburg Polyclinic Hospital; died May 3, aged 81, of coronary occlusion and myocardial infarction.

Duffy, Richard Nixon ✠ New Bern, N. C.; Johns Hopkins University School of Medicine, Baltimore, 1906; fellow of the American College of Surgeons; on the staff of St. Luke's and Good Shepherd hospitals; died April 14, aged 72, of a heart attack.

Farnacy, Nicholas Lester ✠ Cleveland; Western Reserve University School of Medicine, Cleveland, 1921; fellow of the American College of Surgeons; life member of the Cleveland Museum of Art; a member of the Cleveland Health Museum; on the staffs of the St. Luke's and Woman's hospitals and the Huron Road Hospital, where he died June 8, aged 59, of cancer.

Fedde, Bernhard Andreas, Brooklyn, N. Y.; University and Bellevue Hospital Medical College, New York City, 1900; member of the Medical Society of the State of New York; at one time assistant clinical professor of medicine at the Long Island College of Medicine; consultant in medicine at Kings County Hospital; physician emeritus at Norwegian Lutheran Deaconess Home and Hospital; died June 14, aged 77, of angina pectoris.

Ferguson, John Angus ✠ Wyckoff, N. J.; Long Island College Hospital, Brooklyn, 1896; an associate member of the American Medical Association; formerly member of the board of education in Brooklyn; died in Valley Hospital, Ridgewood, June 9, aged 82, of arteriosclerosis.

Finner, Lucy Louise, San Francisco; Rush Medical College, Chicago, 1930; certified by the National Board of Medical Examiners; died in the San Francisco General Hospital May 29, aged 56, of multiple embolism of the lungs.

Flinn, Charles C. ✠ Allegan, Mich.; Bennett Medical College, Chicago, 1901; died in the Allegan Health Center April 6, aged 78, of uremia.

France, Joseph John, Napa, Calif.; Milwaukee Medical College, 1905; served during World War I; died in the Providence Hospital, Oakland, May 25, aged 78, of acute hemorrhagic pancreatitis.

Frankel, Herbert, Framingham, Mass.; College of Physicians and Surgeons, Boston, 1914; died June 10, aged 66.

Frankenstein, Victor Samuel ✠ Chicago; Northwestern University Medical School, Chicago, 1895; an associate member of the American Medical Association; on the staff of the Michael Reese Hospital and the Woodlawn Hospital, where he died June 15, aged 85, of acute bacterial endocarditis.

Frost, Charles L., Bolivar, Tenn.; Memphis (Tenn.) Hospital Medical College, 1909; died June 1, aged 72, of coronary occlusion and cirrhosis of the liver.

Gore, Samuel Kirkham ✠ Houston, Miss. (licensed in Mississippi in 1922); died in the Houston Hospital June 12, aged 68, of carcinoma of the rectum.

Griggs, Samuel Otis, Fort Thomas, Ky.; Medical College of Ohio, Cincinnati, 1896; member of the Kentucky State Medical Association; for many years health officer of Dayton, where he was on the staff of the Speers Memorial Hospital; died April 1, aged 82, of arteriosclerosis.

Haines, Franklin Gregg ✠ Warren, Pa.; Baltimore Medical College, 1895; for many years county medical director; on the staff of the Warren General Hospital, where he died May 19, aged 83, of chronic cholecystitis and peritonitis.

Hammond, James William, Byron, Calif.; California Medical College, San Francisco, 1897; died in Martinez June 10, aged 98, of arteriosclerosis.

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Hayes, Joseph Owens ✠ Detroit; University of Buffalo School of Medicine, 1947; interned at the Sisters of Charity Hospital in Buffalo; formerly a resident at the Massachusetts Memorial Hospitals in Boston and the Allegheny General Hospital in Pittsburgh; certified by the National Board of Medical Examiners; formerly on the staff of the Veterans Administration Hospital in Buffalo; on the staff of the Jennings Memorial Hospital; died May 27, aged 34, of coronary occlusion.

Hennemuth, John Henry ✠ Emmanus, Pa.; Jefferson Medical College of Philadelphia, 1922; formerly deputy coroner, councilman, and burgess; past-president of the Lehigh County Medical Society; served in the Mexican Border campaign, World War I, and during World War II; died March 30, aged 59, of coronary occlusion.

Hickman, George Lester ✠ Bryant, S. D.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; died June 13, aged 75, of cerebral thrombosis.

Hill, George Ray ✠ Rochelle, Ill.; University of Illinois College of Medicine, Chicago, 1936; interned at the Mercy Hospital in Cedar Rapids, Iowa, and the Methodist Hospital in Fort Wayne, Ind.; served during World War II; died June 11, aged 44.

Hofferkamp, August George ✠ Jeffersonville, Ind.; Loyola University School of Medicine, Chicago, 1926; member of the American College of Chest Physicians and the American Trudeau Society; died in the St. Edward Hospital, New Albany, March 25, aged 62, of cancer of the pancreas.

Horsley, Frederick Melville ✠ Arrington, Va.; Medical College of Virginia, Richmond, 1908; served during World War I; died May 11, aged 80, of coronary thrombosis.

Howe, William R., Youngstown, Ohio; College of Physicians and Surgeons, Baltimore, 1899; died in the North Side Hospital June 20, aged 91, of cerebrovascular accident and arteriosclerosis.

Huffman, James William, Bismarck, Mo.; Medical College of Indiana, Indianapolis, 1905; died April 9, aged 77, of hypostatic pneumonia.

Hulbush, William Albert ✠ Bellingham, Wash.; Indiana University School of Medicine, Indianapolis, 1908; past-president of the Whatcom County Medical Society; formerly chairman of the city health board and county coroner; associated with the state department of public health as screening physician in Whatcom County for public assistance medical services; served during World War I; past chief of staff of St. Luke's Hospital, where he died May 25, aged 70, of coronary disease.

Hunsicker, Hannah Marian, Huntingdon Valley, Pa.; Woman's Medical College of Pennsylvania, Philadelphia, 1902; public school doctor; died April 8, aged 90, of carcinoma.

Hunter, Edward R. ✠ Delanco, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1914; an associate member of the American Medical Association; health officer; on the staff of Burlington County Hospital in Mount Holly; died in the Presbyterian Hospital, Philadelphia, June 6, aged 67, of heart disease.

Huntington, Harry Gilbert ✠ Howell, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1912; for many years city health officer; for 12 years served on the school board; died June 6, aged 70, of acute congestive cardiac failure.

Jahiel, Richard, New York City; Université de Paris Faculté de Médecine, France, 1927; served in the French Army during the early part of World War II; on the staff of the Montefiore Hospital; died June 1, aged 56, of carcinoma of the stomach.

Jordan, Peter Andrew ✠ Santa Jose, Calif.; Jefferson Medical College of Philadelphia, 1901; specialist certified by the American Board of Otolaryngology; member of the Pacific Coast Oto-Ophthalmological Society; an associate member of the American Medical Association; past-president of the Santa Clara County Medical Society; served during World War I; on the staff of the Santa Clara County Hospital, O'Connor Hospital, and San Jose Hospital; died June 1, aged 84, of a heart attack.

Kautz, William Shaw, Cincinnati; Miami Medical College, Cincinnati, 1905; on the staff of the Jewish Hospital, where he died June 5, aged 75, of coronary artery sclerosis.

Lee, George Herbert ✠ Denver; Denver and Gross College of Medicine, 1905; an associate member of the American Medical Association; served on the staffs of the St. Anthony, General Rose Memorial, Presbyterian, and Beth Israel hospitals; died May 31, aged 77, of cerebral thrombosis and arteriosclerosis.

Lynch, George Vincent ✠ Oshkosh, Wis.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1917; fellow of the American College of Surgeons; past-president of the Winnebago County Medical Society; chief of surgery at Mercy Hospital; died in the Jackson Memorial Hospital, Miami, Fla., April 28, aged 68, of septicemia.

McDonald, William Brown, Dixon, Ill.; Hering Medical College, Chicago, 1910; died June 8, aged 90, of arteriosclerotic heart disease.

McNair, Lawrence N. ✠ Albion, Mich.; Detroit College of Medicine, 1911; during World War I assigned as medical officer to the Student Army Training Corps unit at Albion College; on the staff of the James W. Sheldon Memorial Hospital, where he was president of the medical staff in 1942, secretary of the staff in 1952, and vice-president in 1953, and where he died June 14, aged 68, of extensive posterior coronary infarction and bronchiectasis.

Matthews, John Calvin ✠ Huntington, W. Va.; North Carolina Medical College, Charlotte, 1913; fellow of the American College of Surgeons; on the staffs of Guthrie Hospital and St. Mary's Hospital, where he died May 31, aged 69, of myocardial infarction.

Newton, Robley Dunglison, Fort Myers Beach, Fla.; Medico-Chirurgical College of Philadelphia, 1896; died in the Lee Memorial Hospital in Fort Myers April 4, aged 84, of shock.

Offenthal, Adolph W. ✠ New York City; Université Libre de Bruxelles Faculté de Médecine, Belgium, 1913; died April 26, aged 66, of cerebral hemorrhage.

Oginz, Philip ✠ Brooklyn, N. Y.; Long Island College Hospital, Brooklyn, 1908; associate member of the American Medical Association; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; member of the Brooklyn Gynecological Society; on the staffs of the Beth-El and Kings County hospitals; died April 22, aged 69, of arteriosclerotic rupture of an aortic aneurysm.

Pardee, Charles Arthur, Fort Myers, Fla.; Northwestern University Medical School, Chicago, 1927; interned at the Wesley Memorial Hospital in Chicago; served during World War I; member of the American Academy of General Practice; died April 22, aged 59, of coronary occlusion.

Resnik, Ernest David ✠ Brooklyn, N. Y.; Long Island College Hospital, Brooklyn, 1922; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; on the staffs of the Caledonian and Maimonides hospitals; on the staff of the Coney Island Hospital from 1922 to 1927; died June 20, aged 58, of carcinoma of the pancreas.

Ridge, Frank Isaac, Kansas City, Mo.; Columbia University College of Physicians and Surgeons, New York, 1910; assistant clinical professor of medicine at the University of Kansas School of Medicine, Kansas City, Kan.; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; on the staffs of St. Luke's and St. Mary's hospitals; died March 24, aged 69, of rupture of esophageal varices and cirrhosis of the liver.

Roberts, John Charles ✠ Peoria, Ill.; College of Physicians and Surgeons of Chicago, 1887; honorary member of the staff of Proctor Hospital; died June 19, aged 93, of glomerulonephritis and arteriosclerosis.

Ross, Archibald Charles, Albion, Maine; Medical School of Maine, Portland, 1909; local health officer; on the staff of the Thayer Hospital in Waterville; died May 24, aged 73, of coronary thrombosis.

St. Amant, Guy Stanhope ✦ Gonzales, La.; Tulane University of Louisiana School of Medicine, New Orleans, 1911; member of the American Academy of General Practice; died in Our Lady of the Lake Hospital, Baton Rouge, May 26, aged 71, of mesenteric thrombosis.

Salmon, Leon Trudeau, New Hope, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1898; died in Glen Cove, N. Y., April 6, aged 79, of arteriosclerotic heart disease.

Schiffman, Fredric Chace, Baltimore; University of Pennsylvania School of Medicine, Philadelphia, 1954; intern at the University of Maryland Hospital; died April 6, aged 24.

Schlatmann, Vincent Henry, Plainfield, N. J.; Georgetown University School of Medicine, Washington, D. C., 1928; served during World War II; on the staff of the Veterans Administration Hospital in East Orange; died May 29, aged 51, of coronary thrombosis.

Schulz, Arthur Paul Erich, St. Charles, Mo.; Washington University School of Medicine, St. Louis, 1912; died in St. Joseph's Hospital May 7, aged 73, of carcinoma of the larynx.

Scott, Samuel Avery, Amarillo, Texas; Western Reserve University School of Medicine, Cleveland, 1947; for two years served in the medical reserve corps of the U. S. Army; interned at the Southern Baptist Hospital in New Orleans; served a residency at the Veterans Administration Hospital, John Gaston Hospital, and the Baptist Memorial Hospital, all in Memphis, Tenn.; died in the Northwest Texas Hospital June 18, aged 30, of acute myocarditis and peritonsillar abscess with septicemia.

Shrimpton, Elizabeth Latimer, Syracuse, N. Y.; Syracuse University College of Medicine, 1901; died June 6, aged 79, of senility.

Simmerman, John Walter, Roanoke, Va.; Maryland Medical College, Baltimore, 1911; for many years member of the school board; member of the Medical Society of Virginia; on the staff of the Shenandoah Hospital; died May 25, aged 67, of acute coronary occlusion.

Smith, John William ✦ Milwaukee; Marquette University School of Medicine, Milwaukee, 1915; member of the American Academy of Dermatology and Syphilology; formerly on the faculty of his alma mater; past-president of the state board of medical examiners; at one time treasurer of the State Medical Society of Wisconsin; died June 19, aged 63, of pulmonary embolism.

Soles, Fred Arthur ✦ Platteville, Wis.; the Hahnemann Medical College and Hospital, Chicago, 1903; died in Marshfield May 18, aged 81, of coronary thrombosis.

Stamey, James Thomas ✦ St. Joseph, Mo.; Central Medical College of St. Joseph, 1897; died June 20, aged 82.

Stitt, Richard Marks ✦ St. Petersburg, Fla.; Duke University School of Medicine, Durham, N. C., 1946; interned at Duke Hospital in Durham, N. C.; served in the U. S. Naval Reserve on Truk Island in the South Pacific from 1947 to 1949; certified by the National Board of Medical Examiners; on the staffs of the Mound Park and St. Anthony's hospitals; died April 13, aged 34, of hypertension.

Stubenrauch, Charles Henry Sr. ✦ Havana, Ill.; Johns Hopkins University School of Medicine, Baltimore, 1907; died in a Quincy hospital June 21, aged 74, of coronary disease.

Swope, Oscar Clinton ✦ Kingston, Mass.; Boston University School of Medicine, 1902; for many years chairman of the school committee and first school physician; served on the board of the Jordan Hospital in Plymouth, where he was a member of the board of trustees of the Plymouth Five Cents Savings Bank; died June 3, aged 78.

Terrell, Thomas K. ✦ Lynchburg, Va.; University of Virginia Department of Medicine, Charlottesville, 1895; died June 4, aged 85, of pyelonephritis and pulmonary tuberculosis.

Thornton, John Thruston ✦ Charlottesville, Va.; Medical College of Virginia, Richmond, 1902; member of the American Academy of Pediatrics; fellow of the American College of Physicians; died May 30, aged 79, of arteriosclerosis.

Tyson, John Joyner ✦ Durham, N. C.; Medical College of Virginia, Richmond, 1928; fellow of the American College of Surgeons; assistant professor of hospital administration at Duke University School of Medicine; served on the staffs of various administration posts; manager of the Veterans Administration Hospital, where he died May 27, aged 57, of coronary artery disease.

Wahle, George Henry ✦ Boise, Idaho; Washington University School of Medicine, St. Louis, 1919; fellow of the American College of Surgeons; senior member of the American Goiter Association; member and past-president of the Southwest Idaho Medical Association; member and past-president of the staff, St. Alphonsus Hospital; on the staff of St. Luke's Hospital; died June 20, aged 61, of carcinoma.

Wahrer, Carl William, El Dorado, Calif.; Rush Medical College, Chicago, 1902; died May 29, aged 76, of carcinoma of the cecum.

Waligora, Stanley B., Cicero, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1915; died June 13, aged 68, of coronary occlusion.

Wallace, Charles James, Two Harbors, Minn.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1904; died April 16, aged 81, of carcinoma of the stomach.

Wang, Israel ✦ Port Chester, N. Y.; Long Island College Hospital, Brooklyn, 1913; specialist certified by the American Board of Internal Medicine; emeritus attending physician at the United Hospital, where he died April 26, aged 69, of coronary thrombosis.

Ward, Hugh John ✦ Hazleton, Pa.; Jefferson Medical College of Philadelphia, 1944; interned at the Nazareth Hospital in Philadelphia; served in the China-Burma-India Theatre during World War II; served on the staff of the Shamokin (Pa.) State Hospital; died June 3, aged 43.

Watson, Nowlin ✦ Clarksville, Texas; Kentucky School of Medicine, Louisville, 1901; veteran of the Spanish-American War; for many years city health officer; past-president of the Rotary Club; on the staff of the Red River County Hospital, where he died June 8, aged 76, of diabetes mellitus.

Wellman, Clarence Lovejoy, Grove, Okla.; Kansas City (Mo.) Medical College, 1901; veteran of World War I; died June 12, aged 77, of coronary occlusion.

Wells, Milo C., Grove, Okla.; University of Louisville (Ky.) School of Medicine, 1929; died in St. John's Hospital, Joplin, Mo., June 16, aged 55, of coronary occlusion.

Wiebe, Dietrich Vergil ✦ Sacramento, Calif.; University of Kansas School of Medicine, Kansas City, Kan., 1925; interned at the San Joaquin General Hospital in French Camp; area medical officer for the Bureau of Indian affairs; at one time a medical missionary in China; served as board member of the Reedley (Calif.) Hospital; died in San Francisco March 25, aged 67, of coronary occlusion.

Wilkerson, Leonard Boyce, Shorter, Ala.; Kentucky University Medical Department, Louisville, 1902; died in Montgomery April 20, aged 80, of circulatory failure.

Williams, Leonidas ✦ Lewisburg, W. Va.; University of Virginia Department of Medicine, Charlottesville, 1939; interned at the Wheeling (W. Va.) Hospital; died June 26, aged 46, of acute myocardial infarction.

Wilson, Dilimus Wesley ✦ Fort Payne, Ala.; Chattanooga (Tenn.) Medical College, 1900; on the staff of the DeKalb County General Hospital; died June 6, aged 83, of hypostatic pneumonia, osteoarthritis, and myocarditis.

Winter, Joseph Augustus, Leonia, N. J.; Marquette University School of Medicine, Milwaukee, 1937; member of the Association for the Study of Internal Secretions; served during World War II; died in the Englewood (N. J.) Hospital June 9, aged 44, of a coronary attack.

Woodall, Percy Hogan, Homewood, Ala.; University of Nashville (Tenn.) Medical Department, 1896; died April 12, aged 80, of arteriosclerotic cardiovascular disease.

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FOREIGN LETTERS

AUSTRIA

Acute Leukemia in Adults.—At the meeting of the Society of Physicians in Vienna on March 4, Braunsteiner and Reimer reported on a 73-year-old woman and a 35-year-old man with acute leukemia who obtained complete, long-lasting remissions with 6-mercaptopurine. Therapeutic success in elderly patients with acute leukemia is rare. The smallest adequate dose is recommended as the therapeutic principle.

Animal Experiments Concerning Vagus Death.—At the same meeting Dr. H. Kolder reported on the cause of death in explosive decompression, a form of death for which the term shock death is suggested. The cause is a pressure wave of known amplitude and duration. It can be proved that the pressure wave attacks the thorax and the lung respectively. There damage is done by which receptors in the lung are stimulated; the stimulus then is transmitted by the vagus nerve to the respiratory center and an irreversible cessation of respiration results. The changes in the lung alone do not threaten life, therefore vagotomized animals can survive the exposure to pressure waves. Anesthesia or covering the thorax with rubber foam also prevents this "vagus death."

Etiology of Congenital Cardiac Defects.—At the same meeting Navratil, Wenger, and Kaindl reported on a series of 100 mothers of patients with congenital cardiac defects and 200 mothers of healthy children who served as controls. It was shown that hormonal disturbances of the mother, which particularly affect the function of the ovaries, predispose to congenital cardiac defects. A significantly increased incidence of late menarche, tendency to repeated spontaneous abortion, temporary sterility, and irregular menstruation was observed in the mothers of children with congenital defects. Other factors consisted of multiparity and advanced age of the mother at the time of parturition. Children with congenital cardiac defects have a larger number of siblings than healthy children of the average population do. If hereditary influences might play a part in the origin of congenital cardiac defects, then it seems most likely that a hereditary hormonal weakness is transmitted. The arrest of development could result from the concurrence of the hormonal disturbance of the fetus and that of the mother.

Idiopathic Epilepsy.—At the same meeting Dr. E. Niedermeyer of Innsbruck discussed the question whether today one still is justified in speaking of idiopathic epilepsy. Electroencephalograms show that some forms of epilepsy do not have their origin in cortical lesions but suggest a functional disturbance of the diencephalic apparatus, for which Penfield and Jasper of Montreal have coined the collective term of "centrencephalon." It is suggested that idiopathic epilepsy is primarily a centrencephalic dysfunction. The three most important factors in epilepsy are: (1) predisposition to convulsions, (2) irritative noxae, and (3) a convulsion eliciting factor. The predisposition to convulsions means a dispositional defect of the cerebral protective mechanisms against the tendency to hypersynchronous-epileptogenic discharge of ganglion cells. This predisposition is especially important in idiopathic epilepsy. Irritative noxae are predominant in the symptomatic forms, but the predisposition to convulsion may also be present. With certain reservations the designation "idiopathic-symptomatic" may still be used.

Shock Therapy in Childhood Psychosis.—At the meeting of the Society of Physicians of Vienna on May 13, Hift and Spiel reported the case of a girl who, at the age of 13, had been subjected to electroshock therapy. An endogenous psychosis had been definitely diagnosed, and the severity of the psychosis justified the treatment. The electroshock therapy, which was carried out under constant control of psychological tests, was successful. Subsequent examinations revealed that no irreversible damage had been caused. Thus shock therapy seems to be indicated even in children, in selected cases.

Glycogen Storage in Diabetic Patients.—At the same meeting Dr. A. Beringer said that he determined the glycogen content of the liver of animals with alloxan diabetes after they had been given injections of regular insulin, protamine zinc insulin, insulin with retarded action, and depot insulin. Repeated injections of small quantities of insulin produced a greater deposition of glycogen than did large quantities of insulin. Under the influence of protamine zinc insulin more glycogen was deposited in the liver than was the case with corresponding doses of regular insulin. The insulin with retarded action and depot insulin had an intermediate action in this respect. It could be demonstrated by means of puncture biopsy of the liver that these results are applicable also to diabetes in human beings. Thus, when diabetic patients have complications in which an increased glycogen content of the liver is desirable, treatment with protamine zinc insulin, retarded action insulin, or depot insulin seems preferable to treatment with regular insulin.

BRAZIL

Serial Sections in Uterine Cervical Atypias.—Drs. Alberto Rocha and Lucy Teixeira of the histopathological laboratory of the gynecologic department, Minas Gerais State University, at Belo Horizonte report in *Anais brasileiros de ginecologia* (**20**:1, 1955) a series of 33,820 sections made from 101 biopsy specimens and 29 amputated cervices. Among the biopsy specimens, 24 were from patients with stage O cancer whose diagnosis was made by means of histopathological examinations of nonserial sections, before the inauguration of the new laboratory. The 24 histological blocks of the biopsy specimens were reexamined by serial sections, which resulted in the finding of two cases already presenting signs of invasion, invalidating their classification as stage O cancer. One of these two patients had been treated by radium and died five years after the diagnosis of cancer was established. The other, who was treated by simple total hysterectomy, was in good condition six years after the diagnosis was established. Review of the 24 specimens revealed O stage cancer in 15 cases; initial invasion in 2; slight atypia in 2; cervicitis in 2; and insufficient material in 3. A review of the 14 biopsy specimens in the whole series that showed simple atypia confirmed this diagnosis in 11 cases; one was classified cancer stage III, 3b; one, cancer stage Ib with suspicion of IIIB; and one had epithelial hypertrophy and cervicitis. After the inauguration of the new laboratory, 10,464 sections were examined from 61 biopsy specimens. The serial sections from 40 of these revealed simple atypia in 2 cases; increasingly atypical epithelium (stage O cancer) in 2; epithelioma in 4; epithelial perforation in 4; regressive changes in 11; insufficient material in 7; acute condyloma in one case; and normal epithelium in 9. Among the 29 cervices removed, 11 showed stage O carcinomas and 18 showed normal epithelium. In only one was a more marked atypia than that disclosed by the previous biopsy found.

Diffuse Scleroderma.—Dr. J. Aguiar Pupo in *Revista do Hospital das clinicas* (**10**:1, 1955) analyzed a series of 13 cases of diffuse scleroderma. Seven of the 13 patients were female and 6 were male in contrast to the marked predominance of female patients that is considered a rule in this disease. Only one patient was more than 60 years old; two were more than 40; and the rest were under 35. The onset was preceded by Raynaud's phenomenon in four patients and by varying degrees of edema and pains in the joints in nine. Scleroderma of the

The items in these letters are contributed by regular correspondents in the various foreign countries.

extremities was seen in all but one. Diffuse abnormal pigmentation was found in four patients and areas of poikiloderma in three. The esophagus was involved in six patients, the heart in three, the lungs in two, and the intestines in three. The radiological study of the skeleton disclosed a diffuse demineralization, while in the extremities osteoporosis was frequently noted, with narrowing of the articular spaces or bone absorption of the last phalanges. Alterations in the nervous system were not found, except in a patient who presented symptoms of psychosis a few days before he died. The basal metabolic rate was determined in seven patients, four presenting increased values. In a patient in whom the basal metabolic rate was increased, the scleroderma began 18 months after thyroidectomy was performed. Alkaline calcium phosphate and inorganic phosphorus levels in the blood were normal in all patients. The globulin level was always increased. Histopathological examinations disclosed the usual changes and frequently the findings of liquefactive degeneration of the basal layer and a variable number of chromatophores full of melanin in the chorion. It was also ascertained that the involvement of the collagenic fibers was not always uniform in the early stages of the process. Thus, in two patients the collagenic tissue of the superficial skin layers was apparently normal, alterations being present only in the deep layers. Fibrinoid degeneration of the collagen or of the vessel walls was not seen. Treatment with cortisone, corticotropin, *p*-aminobenzoic acid, tocopherol, propylthiouracil, pancreatic extract, heparin, and sympathectomy was tried without success. The prognosis of diffuse scleroderma is poor. Death occurred in seven patients after one to five years. The general condition of two patients is not known, but a follow-up of the remaining four indicated that the disease was arrested, although the patients were practically invalids.

Causes of Peritonitis.—Dr. A. Behmer in *Revista do Hospital das Clínicas* (**10:**25, 1955) analyzed 31,000 autopsy reports with the aim of ascertaining the importance of intestinal inflammation as a cause of peritonitis. Peritonitis was classified as caused by nonspecific intestinal inflammations, specific intestinal inflammations, and other causes. There were 582 cases of intestinal inflammation of undetermined cause, but almost all of these presented the pathological features of bacillary dysentery. In this group, 63 cases (10.8%) showed lesions of peritonitis. Intestinal ulcers were the most common, being observed in 337 autopsies, including 245 cases of ulcerative colitis, 44 of ulcerative enteritis, and 48 of ulcerative enterocolitis. Pseudomembranous lesions of the intestines were observed in 150 autopsies, including 93 cases of colitis, 33 of enteritis, and 24 of enterocolitis. The 63 cases of nonspecific intestinal inflammations causing peritonitis involved the small intestine in 26 cases, the colon in 27, and both in 10. There were 50 cases of peritonitis among the 337 autopsies showing intestinal ulcers, or 14.8%, and only 9 among the 150 cases of intestinal pseudomembranous lesions, or 6%. Among the 337 autopsies showing ulcers, the ulcers of the small intestine appeared as the predominant factor in the production of peritonitis, as there were 22 cases of peritonitis among 44 cases of enteritis (50%), while there were only 22 among 245 cases of colitis (9%), and 6 among 48 cases of enterocolitis (12.5%).

A similar study of the group of the pseudomembranous intestinal processes revealed pseudomembranous enteritis in 12.1%, pseudomembranous enterocolitis in 12.5%, and pseudomembranous colitis in only 2.1%. When the ulcers were located in the colon, in a total of 22 cases of peritonitis there were 14 with perforation and 8 without. When the lesion was located in the small intestine, in a total of 22 cases of peritonitis there were 12 with perforation and 10 without perforation. Thus the proportion of cases without perforation is higher in ulcerative enteritis than in ulcerative colitis. In the cases with inflammation of both intestines, in six presenting peritonitis there were two with perforation and four without, such perforations being always observed in the small intestine only. The proportion of peritonitis without perforation is almost the same for the two groups of cases with ulcerative and pseudomembranous inflammation (6 and 6.5% respectively).

In the 31,000 autopsies, there were 1,278 cases of intestinal lesions of a specific character (tuberculosis in 999, amebiasis in 170, typhoid in 41, paracoccidioidomycosis in 36, and venereal lymphogranulomatosis in 32). Of the 1,278 autopsies with specific intestinal lesions, 193 cases (15.1%) were accompanied by peritonitis. The largest number of cases with peritonitis (132) was found in tuberculous group. The second, third, and fourth largest were in the amebiasis, paracoccidioidomycosis, and typhoid groups, with 13.4, 8.8, and 6.7 respectively. Venereal lymphogranulomatosis represented only 2.5% of the cases. If we included tuberculous peritonitis without intestinal lesions we would have a total of 423 cases of peritonitis, 362 being of tuberculous origin, which gives the high proportion of 85.5% of all cases of specific peritonitis. The process that presented the highest proportion of intestinal lesion accompanied by peritonitis was paracoccidioidomycosis with 47.2%, followed, in decreasing order, by typhoid with 31.7%, venereal granulomatosis with 15.6%, amebiasis with 15.2%, and tuberculosis with 13.2%.

Besides the causes of peritonitis in connection with the previous two groups of nonspecific and specific intestinal lesions, there were 792 autopsies presenting peritonitis due to other causes including surgical acts in 259, tumors in 106, appendicitis in 82, diseases of the liver and the biliary ducts in 66, diseases of the genitals in 42, gastric ulcer in 26, duodenal ulcer in 26, megacolon in 18, septicemia in 16, strangulated hernia in 12, myocardial infarction in 6, intestinal obstruction in 5, megaesophagus in 4, less frequent causes in 86, and undetermined causes in 38.

Cancer of the Thyroid.—Cancer of the thyroid is not so rare as was formerly thought, according to Dr. A. Rego in *Revista brasileira de cirurgia* (**29:**31, 1955), who reports a series of 1,231 patients who underwent thyroidectomy for goiter. Of these patients, 56 were found to have cancer. This incidence of cancer varies according to the type of goiter. A higher frequency was observed in nodular goiter (52 cancers in 910 patients) than in toxic diffuse goiter (4 cancers in 321 patients). It is also higher in nontoxic goiter (35 cancers in 470 patients) than in toxic goiter (21 cancers in 761 patients). Among the 910 patients with nodular goiter, the incidence of cancer varied depending on whether the goiter was uninodular or multinodular. In the former there were 39 cancers in 395 patients, and in the latter there were 13 cancers in 515 patients. Dr. Rego found cancer in both toxic and nontoxic goiters, but a higher incidence was discovered in uninodular goiter. Of 470 patients with nodular nontoxic goiter there were 35 cancers, or 7.4%, the incidence for uninodular and multinodular nontoxic goiters being respectively 10.7 and 4.5%, while among 440 patients with toxic goiter there were 17 cancers, or 3.9%, the incidence for uninodular and multinodular toxic goiter being respectively 8.8 and 0.7%. These figures illustrate the markedly higher frequency of cancer in uninodular goiter, be it toxic or nontoxic. These small tumors are precisely the ones that go undetected, or whose surgical removal is generally believed to be contraindicated. They cause little physical inconvenience and small or no functional impairment of the gland, the patient being always grateful to the physician who, erroneously, follows this line of reasoning.

Intestinal Schistosomiasis.—The repeated examination of stools, even by means of the sedimentation technique, will not reveal all cases of intestinal schistosomiasis, because of the small number of schistosomes, or the predominant infestation by parasites of the same sex, or even the advanced stage of the disease. Believing that the epidemiological significance of this fact for the evaluation of the incidence of the disease in endemic areas had never been studied before, Dr. Luis Pereira da Silva and co-workers, of the National Department of Health, made an experimental study in a rural district in the state of Paraíba. An earlier survey of the district showed an infestation index of 8.7% for the age group from birth to 9 years, and 33% for the group 10 years and over. For the present study the authors performed four successive stool examinations and an intradermal test on 67 random persons aged 10 or over who

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showed negative results on first examination. By this method the incidence of the disease was found to be not 33 but 73%. For other intestinal helminths (Ascaris lumbricoides, Trichuris trichiura, Strongyloides stercoralis, Enterobius vermicularis, and Ancylostoma duodenale) the infestation index went up about 50%. The authors conclude that the results of surveys made through only one stool examination do not represent the real incidence of intestinal schistosomiasis. In areas where the disease has long been endemic, if the stool survey reveals the existence of a certain number of persons harboring the parasite and the exposure of the entire population is about equal, the use of adequate diagnostic procedures will probably disclose that most of the population is parasitized. One of the main causes of variation of the infestation index in different localities is the use of nonhomogeneous groups of persons, when these localities lie in a zone where the disease has long been endemic.

New Maternity Hospital.—The Maternity Hospital of São Paulo, which was officially opened on Mother's Day, is the biggest hospital devoted exclusively to obstetrics in South America. The city of São Paulo, which has 3 million inhabitants, needs about 2,000 obstetric beds and with the addition of 500 beds in the new hospital there are now 1,421 such beds available. An increment of about 200 beds each year is needed for the city. The new hospital can accommodate about 26,400 deliveries a year. The nursery has room for 450 patients, of which 40 cradles are for prematures and 15 are in an isolation ward. There are 16 delivery rooms, 8 of which are equipped for major operations.

CHILE

Correlation of Symptoms with Hemodynamic Findings in Mitral Valve Stenosis.—At a meeting of the Chilean Heart Society in 1954, Prof. F. Rojas and his co-workers stressed the importance of making a correct diagnosis of pure mitral valve stenosis and the degree of stenosis, so that the advisability of surgical treatment could be evaluated. In a series of 30 patients with pure or predominant mitral valve stenosis, the average age was 33 years. Eighteen were treated surgically. Paroxysmal dyspnea, pulmonary edema, and hemoptysis were not seen when the mitral orifice had an area of 1.5 sq. cm., but if the area was smaller one or more of these symptoms was present. There was no clear-cut relation between cardiac output and body development. One-third of the patients had cyanosis and/or the typical mitral facies. Although the oxygen saturation was practically normal in all patients, the difference in oxygen saturation between arteries and veins was great in all patients but was slightly greater in the cyanotic group. The decrease in the vital capacity of the cyanotic group was more striking. The arterial blood pressure was compared with the area of the mitral orifice and the cardiac output, and it was found that as the area decreased the systolic pressure and output also decreased proportionately. In all these patients a definite correlation existed between the clinical and hemodynamic findings. A similar correlation could be established with pulmonary capillary pressure. A relationship also existed between the intensity of the second pulmonic sound and pulmonary pressure. The radiographic study of the left auricle and mitral area and the capillary pressure also revealed a definite correlation. Correlation between the size of the right ventricle and pulmonary arterial pressure on one hand and total pulmonary resistance on the other were also noted, as was right ventricular hypertrophy as shown in the electrocardiograms in relation to pulmonary arterial pressure, arteriolar resistance, and area of the mitral orifice.

CUBA

Gout.—In *Revista médica cubana* (vol. 66, no. 3, March, 1955) Dr. J. M. Ballejo said that gout is almost forgotten in Cuba, because it is considered to originate only in foreign countries. None of his 17 patients with the disease gave a family history of gout. All of his patients were white men. Obesity was present in 10 patients in his series, alcoholism in 13, and hypertension in 4. The average age of the patients was 40 years and the duration of the disease varied from a few weeks to 14 years. The initial attack occurred in the large toes, ankles, or both. An average of 12.2 mg. of 17-ketosteroids per 100 cc. was found in 24-hour urine specimens. The determination of the 17-ketosteroid level was of diagnostic value. The drugs used included colchicine, corticotropin, sodium salicylate, aspirin, probenecid, and cinchophen. Cinchophen, because of its toxic effects, must be used with caution. Patients must rest and have a light purine-poor diet with fruit juice, milk, and plenty of water.

Action of Histamine and Salicylates on Rheumatic Conditions.—In the same issue Landa and de Diego state that, since the effects of cortisone and corticotropin on rheumatic joints has been studied, many observations have been made to determine whether the beneficial results obtained by salicylates were produced by a similar mechanism. They showed that salicylates given orally and parenterally acted similarly to corticotropin; that histamine produced an eosinopenia within 90 minutes of its administration similar to but more rapid than that of the hormones and salicylates; and that patients to whom combined histamine and salicylates were administered by iontophoresis showed the same improvement as when corticotropin was used. In a series of 65 patients, 36 had bursitis, 25 calcific tenontitis of the shoulders, and 4 had other types of bursitis. There were 22 healthy control patients. It was found that the good results obtained with iontophoresis with histamine and salicylates were due to the stimulus that salicylates produced on the anterior lobule of the pituitary. Besides the well-known, classic effects of the former, it caused the latter to liberate corticotropin, which in time stimulated the adrenals to produce cortisone, compound F, and other steroids. Histamine and salicylates when given together by iontophoresis act synergistically, producing better results than when only sodium salicylate is used. Histamine given by iontophoresis acts on the eosinophils in the same way as when it is injected.

DENMARK

Bovine and Human Brucellosis.—In *Danish Medical Bulletin* for May, 1955, Axel Thomsen stated that by 1944 the charting of bovine brucellosis had reached such a point that about 25% of all the herds and 11% of the total cattle population in Denmark were found to be infected. In 1946 Denmark adopted the Bang ring test, a sample of milk instead of a sample of blood being used. This simple test is extremely sensitive and can be applied to all the herds in Denmark every third month. Large parts of Denmark are now completely free of the disease, and it is calculated that only about 1% of all the herds are infected as compared with 25% only a few years ago. As a rule, a new outbreak can be suppressed, before any noteworthy damage has been done, by the removal of a single animal. Two years from now there should be only a few isolated cases left, if any. A similar note of justified optimism is sounded in the same issue by Martin Kristensen, with regard to human brucellosis, who shows that, while in 1944 there were 261 such cases, the corresponding figure for 1954 was 33. He notes that the frequency of brucellosis in Greater Copenhagen has decreased since 1942 on an even larger scale and concludes that the effective combating of infectious abortion by veterinarians will mean freedom from the human infection.

Cancer of the Breast.—In *Ugeskrift for læger* for May 19 Dr. Erik Andersson states that it is a measure of our uncertainty over the merits of hypophysectomy for cancer of the breast that this operation has hitherto been reserved for advanced cases that have proved refractory to more conventional methods of treatment. He reports a series of six patients who suffered from advanced disease with metastases to the bones and soft tissues. They had undergone operative, radiological, and hormone treatment without avail, and the severe pain from which they suffered required large doses of morphine. Their disease had been diagnosed from one to six years earlier, and their ages ranged from 38 to 68 years. They were warned that no cure could be guaranteed them by hypophysectomy, which was preceded and followed by cortisone treatment. All six patients stood the operation well, but in one of them, a woman aged 55, bilateral parotitis

and pneumonia developed on the fifth postoperative day. The extensive metastases in the liver may have contributed to her death. Three to four months after the operation the surviving five patients were still free from pain, which had ceased one to three days after the operation. In all of them the sedimentation rate had approached normal levels, and the blood sugar and basal metabolism also showed improvement. Radiological examinations of the metastases showed no regression. The patients felt somewhat tired and their reactions had slowed down slightly, but there was no other psychic change. Their general condition was much improved, and none of them used morphine derivatives as before. Hypophysectomy may achieve a remission if nothing more.

Celiac Disease.—In *Ugeskrift for læger* for April 21 Mette Hertz reports a follow-up study of 31 children treated for celiac disease. Although 2 of them died of this disease and another 2, of fibrosis of the pancreas, 27 of the patients were treated and reexamined from 2½ to 10 years after discharge from hospital when their ages ranged from 4½ to 13 years. None of the patients suffered from severe dyspepsia on reexamination, but 10 were still subject to a slight degree of dyspepsia from time to time. The mental and physical development of the children was so close to normal that it seems justifiable to hope that the acute celiac disease of early childhood will not usually be followed by permanent ill-effects. In the same issue Dr. C. Hansted confirms some of the important observations made by Dicke and his co-workers who have incriminated gluten as being mainly responsible for celiac disease. Hansted has found that gluten from wheat, rye, and oats is detrimental to children suffering from celiac disease and that wheat-starch, corn flour, rice flour, buckwheat, peas, beans, potatoes, various vegetables, meat, and fish are tolerated. Healthy children from 5 months to 10 years old did not react to the administration of gluten, but some infants less than 3 months old reacted to it with dyspeptic symptoms and one of them with increased fat excretion. Hansted's prolonged fat-balance tests have shown that various forms of pure starch are well tolerated by patients with celiac disease, whereas small quantities of flour containing gluten aggravate the fat absorption and clinical manifestations of the disease.

Of What Do Soldiers Die in Peacetime?—In *Ugeskrift for læger* for May 12 Dr. J. B. Dalgaard has investigated the causes of death of 211 soldiers and 97 officers of the Danish Army and Air Force. Serving as controls were the deaths in a normal cross section of the male population of the same age in Denmark. The average age of the officers being much higher than that of the soldiers, it is not surprising to find heart disease, apoplexy, and malignancy figuring more prominently among the former than among the latter, but it is disquieting to note how frequent suicides were among both the military and the control groups. The death rate from this cause among the soldiers was 16% compared with 19% in the controls. Dalgaard has scrutinized the motives for suicide in the military services in the hope of discovering those that can be eliminated by administrative precautions. He has found the conditions of army service responsible for suicide in only three cases, motives of a more personal character being in the overwhelming majority. Broadly speaking, his investigation shows that deaths from natural causes are more rare among soldiers than among civilians, whereas the reverse is the case with regard to accidental deaths due to drowning, explosions, and traffic accidents.

Death of Professor Abrahamsen.—Prof. Harold Abrahamsen, Denmark's leading urologist, was born in 1885. After serving a surgical apprenticeship in many fields he was put in charge of department D of the Bispebjerg Hospital in 1927. This appointment gave him an opportunity to exercise his gifts as a teacher and to develop orthopedic surgery. In 1934 a trip to the United States did much to promote his interest in urology. His 60th birthday was celebrated by the issue of a *Festskrift* containing many articles of general as well as surgical interest. His death on April 20, 1955, was due to cancer of the colon with metastases.

ENGLAND

Rising Cost of Health to the Nation.—At a meeting of the West London Medico-Chirugical Society, Sir John Charles, Chief Medical Officer of the Ministry of Health, stated that the cost of health to the nation has increased steadily since the National Health Service was established. The cost of running the hospitals in the five year period has increased by 32%; salaries of physicians by 27%; salaries of nurses by 37%; and all other salaries and wages by over 47%. Medical staffs have increased by about 18%, nursing staffs by 14%, and administrative staffs by 12%, although there has been hardly any increase in the total number of hospital beds. These were occupied for about 90% of the time, but the turnover has increased from 6.5 to 7.5 patients per bed per year. Hospital inpatients have thus risen from nearly 3 million a year when the Health Service was started to 3,500,000. Delay in filling beds, in starting diagnostic procedures, in starting treatments, and in discharging patients has led to the uneconomic use of beds. Nearly 19,000 general practitioners now attend about 42,400,000 persons, a ratio of 2,330 patients per panel physician. Sir John urged greater economy in prescribing drugs, which cost 88 million dollars annually when the Health Service began but now cost 118 million dollars, an increase of 34%. The most striking changes were in the proportions of mixtures and proprietary preparations. At the beginning of the Service, mixtures accounted for 34% of all prescriptions and proprietary preparations for 16%. Now mixtures have dropped to 24%, and proprietary preparations have risen to 27%. The cost of the pharmaceutical services, 137 million dollars annually, is now nearly as much as the general medical service, which costs 148 million dollars. The number of prescriptions issued a year is 220 million, or over 5 prescriptions a year for every person making use of the Health Service. The average cost per prescription is 60 cents. Sir John believes that some of this prescribing is not strictly necessary. Smaller quantities of drugs could often be prescribed, and some drugs not used could be returned to the pharmacy instead of being thrown away. Antibiotics are probably being abused. At first their use was restricted to the hospitals and treatment was kept under bacteriological surveillance. They are now used indiscriminately when other and less expensive preparations would suffice. It is doubtful that the average proprietary preparation has a greater therapeutic action than the standard one, but there are undoubted exceptions. If the Health Service is to succeed, waste must be eliminated.

Medical Litigation.—A 35-year-old hemophiliac was awarded additional compensation on account of his disability. While driving his van in London he was involved in a minor collision with an ambulance belonging to the London County Council. The accident, which would normally have been trivial, caused bleeding into his hip and knee joints. He was awarded $8,400 special damages and costs. In a normal person the compensation in this case would have been minimal, but the court took the view that liability was not limited to the normal consequences of a negligent act.

Another case concerned a 9-year-old girl who suffered from burns due to an overturned inhaler containing boiling water. She was under treatment for poliomyelitis in a children's ward and had only limited use of her hands and arms. She was given an inhaler containing boiling water for her bronchitis. This was placed on a tray resting on a pillow over her knees. The inhaler was satisfactorily used for two months in this fashion without mishap. One morning when the nurse left the ward for a few moments the inhaler was upset and the child was scalded. Her mother brought an action for negligence against the hospital. The judge held that neither the nurse nor the hospital administration was negligent, since the positioning of the inhaler and the child had been satisfactory. The nurse was responsible for the care of 16 other children. This opinion was upheld in the Court of Appeal.

A patient complaining of pains in the chest went to a hospital in Liverpool. The physician, who was an intern, gave him two tablets of codeine and told him to return later for radiological examination. A quarter of an hour later the patient was found dead near the hospital, death subsequently found to be

due to coronary thrombosis. The patient's widow brought an action for damages against the physician and the hospital. The fact that the intern spent an hour examining the patient showed that, although he made a mistake in diagnosis, he was not negligent. After hearing medical witnesses the judge said that the intern was not negligent in rejecting coronary thrombosis as a diagnosis and therefore was not negligent in sending the patient home. The judge added that even if rest had prolonged the patient's life the prognosis would still have been poor and the patient's future as a breadwinner would not have been bright.

Induced Hypothermia.—On April 1 the Section of Anesthetics of the Royal Society of Medicine debated the present status of induced hypothermia. Dr. C. F. Scurr of London said that hypothermia reduced cell metabolism in a linear fashion so that cells could survive anoxia for longer periods. The circulation of the brain in an animal at a temperature of 77 F (25 C) could be completely occluded for 20 minutes without physiological or histological damage to the brain. Recently a case had been reported of a complete circulatory arrest in a child for 22 minutes at a temperature of 71 F in whom there was no evidence of cerebral damage 30 hours after operation. The hypothermic technique is valuable for intracardiac operations requiring an open heart, temporary occlusion of the venae cavae, and cessation of the circulation; for operations in certain congenital cardiac anomalies in which there is cyanosis or the great vessels need transplantation; in cranial operations involving the temporary arrest of part of the circulation of the brain; in certain neurosurgical procedures; and in operations on the great vessels supplying vital organs. Under normal circumstances the kidneys and spinal cord withstand barely 30 minutes of ischemia, but under induced hypothermia at 80.6 to 82.4 F (27-28 C) up to two hours is tolerated. The advantages to be gained from the technique include (1) reduction of the oxygen requirements of the tissues, since if shivering is prevented oxygen consumption falls; (2) reduction of cardiac work; (3) increase in the coagulation time of the blood, which may be beneficial where thrombosis is a hazard; (4) decrease in the amount of anesthetic needed; and (5) reduction of bacterial and enzyme activity.

There are, however, disadvantages such as the increased irritability of the myocardium, which might cause spontaneous ventricular fibrillation. Because of this, continuous electrocardiographic control is essential, as the appearance of arrhythmias or ectopic foci is a danger signal. The exact cause of fibrillation is not fully understood. A possible explanation is that during hypothermia the formation of acetylcholine is depressed, so that the pacemaker loses its dominance and ectopic foci appear. This explains the beneficial effect of neostigmine in preventing ventricular fibrillation. Hyperventilation, with carbon dioxide absorption, helps to reduce the incidence of cardiac irregularities during hypothermia. Other disadvantages are a shift to the left in the oxyhemoglobin dissociation curve, retardation in the elimination of anesthetic agents, production of the stress response to cold, and increased viscosity of the blood. During rewarming, "after-cooling" may occur owing to the opening up of the peripheral circulation with the transfer of very cold blood to the main circulation. A further fall in the central temperature from this cause may lead to ventricular fibrillation.

Dr. Scurr uses a cooling blanket to lower the temperature of the body. The patient is anesthetized with ether, cyclopropane, or thiopentone–nitrous oxide-oxygen and a muscle relaxant to prevent shivering. The body is then wrapped in a blanket through which water circulates at 35.6 to 39.2 F (2-4 C). Before the desired temperature is reached, warm water is circulated through the blanket to prevent the body temperature from falling any further after the cooling process ceases.

Dr. Cecil Gray of Liverpool described his results with induced hypothermia in 110 patients. In the first 40 patients the French technique, with the use of intermittent doses of chlorpromazine, pethidine, and promethazine, was employed, but this has been abandoned because of the long time needed to lower the temperature and the difficulty in controlling shivering. He now induces light anesthesia with thiopentone sodium, nitrous oxide, and oxygen, prevents shivering with *d*-tubocurarine, and aids cooling with moderate doses of chlorpromazine. The body is cooled with ice bags or a cooling blanket. The patient's position is changed every 15 minutes to prevent pooling of blood and "after-cooling" that commonly occurs in patients with a large surface area. Adequate cooling for one and a half hours can be obtained. Dr. Gray induces hypothermia for intrathoracic, neurosurgical, and general surgical operations. In neurosurgery it may be used for long periods with the patient in the upright position; in general surgery a low temperature protects against the effects of surgical trauma, particularly in poor-risk patients. There were 13 deaths in 110 patients, most of whom were poor surgical risks, but 3 were due to pulmonary embolus. Dr. Gray does not believe that cooling is necessary in patients with congenital heart disease undergoing a Blalock's anastomosis, and investigation of his patients undergoing hypothermia did not confirm the view that pituitary-adrenal responses were modified by cold. On the other hand an investigation in dogs suggested that inhibition of the stress response might account for some of the benefits of hypothermia. Hypothermia is a special technique, with definite risks, and should only be used in specially equipped centers.

Who Pays?—A resident on the lonely Scottish island of Ailsa Craig urgently needed medical attention, and on two occasions the local lifeboat was hired to take him to a physician on the mainland. The Ayrshire Medical Executive Council, under the National Health Scheme, met the expense of $45 out of the physician's local mileage fund on the grounds that if the patient had not come to the physician the latter would have gone to the patient, and an arrangement was made to hire the lifeboat in emergencies and pay for it out of the mileage fund for Ayrshire. The Department of Health for Scotland, however, confirmed the view of its auditors that there was no provision under the National Health Service Act to pay the cost of transporting a patient to a physician and, since the patient had not attended a hospital, the cost could not be charged to the ambulance service. The department suggested that the patient should be asked to pay, but this was ignored. Accordingly the department recommended that the local medical committee be asked to agree to the money being paid out of the mileage fund for Ayrshire. The committee, however, refused to accept this proposal, and the executive council has now, at the suggestion of the Department of Health, made application for the amount to be made a first charge on the mileage fund for Scotland.

Training of Nurses.—Owing to the lack of recruitment in the nursing profession, the Scottish Standing Nursing and Midwifery Committee has suggested an experimental two year course and a three year comprehensive course (Work of Nurses in Hospital Wards, London, Her Majesty's Stationery Office, 1955). The two year course might be tried for five years to assess its value. Student nurses would live in a building apart from the hospital, where they would receive their theoretical training and enjoy a corporate life like a resident university student. Ward training would be received in appropriate hospitals nearby. The nearest approach to this at present is the nurses' home attached to some of the larger hospitals. Student nurses should be carefully selected, should have attained a good educational standard, and should not be less than 18½ years old. In any one center the intake should not exceed more than 30 students a year, and to this number there should be allotted three nurse tutors and two clinical instructors. The latter represent a suggested new grade, with a status of ward-nurse with some experience in teaching. The curriculum should include medical, surgical, gynecologic, psychiatric, pediatric, ophthalmologic, dermatological, otorhinolaryngolical, obstetric, infectious disease (including tuberculosis), operating room, and domiciliary nursing. At the moment teaching is rather haphazard and disconnected; if a nurse is busy or on night duty, she may miss important lectures or demonstrations.

A three year course, the same length as the present one, conducted in a hospital or group of hospitals already training nurses is also suggested. Student nurses would obtain experience in general and specialized nursing fields. This plan would give the student nurse experience in those branches she would not normally encounter in general training, such as mental disease, infectious disease, and tuberculosis. Another recommendation is to try the team system, whereby the patients are divided into

groups of 10 or 12, and each group assigned to the care of a small team of nurses, comprising a staff nurse, a nurse in training, and a nursing auxiliary. At the moment twice this number are often cared for by only two nurses by day and one at night. The assignment of a group of patients to such a team has already been tried in some hospitals. The objection is that at off-duty times there are no nurses for a particular group of patients and a relief team has to take over. This calls for a larger supply of nurses than exists at the moment.

Scotland's Health in 1954.—In 1954 there were fewer deaths in childbirth and from tuberculosis than ever previously recorded and a continued lowering of the death rate among children under 5 years of age. The incidence of sickness as measured by attendances at hospitals and visits to physicians is, however, still high. There were more than 2 million new hospital outpatients during the year, with total outpatient attendances reaching nearly 7 million and inpatients numbering 500,000. These figures are for a population of about 5,500,000. There was a rise in the death rate of men aged 50 to 64. In the age group 55 to 65, deaths from respiratory cancer were six times as common as two decades ago, and coronary thrombosis was six and one-half times as common. Bronchitis increased by nearly 25%. These figures are for males. The death rate among females of all ages was lower than two decades ago.

Hospital accommodations and hospital staffs have been increased to cope with the call on the health services by the public. By the end of 1954 beds had increased by 9% compared with figures at the beginning of the National Health Service, and the number of nurses rose from 19,000 to 24,000. There was also a rise in the number of hospital specialists. Running costs of the hospital and specialist services in Scotland increased from 69 million dollars in 1949-1950 to $84,500,000 in 1953-1954. These figures were small in comparison with the increased hospital attendances.

The birth rate, 180 per 1,000 population, was higher than it has been for four years. Infant mortality was 31 per 1,000 births and was the same as in 1953, the lowest on record. The stillbirth rate, 25 per 1,000, was also the same as in 1953. The death rate of 12 per 1,000 population was 0.3 below the average of the previous five years. The number of deaths from the principal epidemic diseases was 254, which was 133 fewer than in the previous year.

Factors Affecting Infant Mortality.—The Social Medicine Research Unit of the Medical Research Council and the General Register Office of London have made a joint inquiry into some of the social and biological factors affecting infant mortality in Britain (*Lancet* **1**:341; 395, 1955), which is still high. The number of stillbirths last year was nearly 16,000; deaths in the first week of life numbered about 10,000; and the postneonatal mortality was 8,000. The total of 34,000 deaths was 6% of all deaths, but because they occurred at the beginning of life they represent more than 6% of the total wastage of life caused by untimely deaths. Heady and his co-workers, investigating stillbirths and infant deaths for 1949 and 1950 in England and Wales, found that the stillbirth rate rose with age for mothers of any given parity, but the postneonatal death rate decreased with the age of the mother up to 35 years. The stillbirth rate of infants of mothers of a given age was high for the first-born, fell for the second-born and third-born, and rose thereafter. The postneonatal death rate for infants of mothers of a given age, on the other hand, rose steadily with increasing parity. The neonatal death rate varied less than the other two rates and occupied an intermediate position.

These rates were the same in all social classes. Since large families are associated with a relatively high postneonatal death rate, and since families have decreased in size and the postneonatal death rate has fallen from 91 per 1,000 in 1906 to less than 10 today, it is natural to inquire whether the reduction in family size accounts for an important part of the fall in the rate. Figures collected by the Social Medicine Research Unit workers show that change in family size by itself has only made a small contribution to the postneonatal death rate. The fall must be attributed mainly to increased knowledge by mother and doctor of infant care. The strong relationship that emerges from this survey between maternal age and parity and the postneonatal death rate is of interest. It is well known that age and parity are related to the stillbirth rate. This is not surprising, since these factors are related, and possible connections between the maternal, placental, and fetal pathology may be envisaged. A relation between age and parity and later mortality does not follow so closely from these considerations. It is more interesting, therefore, that these factors do not affect postneonatal mortality and that the effect is so different. Stillbirths and postneonatal deaths thus appear to have different causes and quite distinct variations with age and parity. Postneonatal deaths are due mainly to infections, and as might be expected the deaths from infection are related to the mother's age and parity in much the same way as the total deaths at this age are. These trends of postneonatal deaths with age, parity, and social class may furnish clews to the spread and control of these infections. Three possible explanations present themselves: increased opportunity for infection in a large family; economic consequences of a large family; and the ability or inability of young mothers with large families to cope with their babies. At least three vulnerable groups appear from the data of the survey: mothers over 35 bearing first babies have a high risk of stillbirth; mothers over 40 of any parity have a high risk of stillbirth; and babies of young mothers with large families for their age have a high risk of death in the postneonatal period.

Treatment of Service Personnel on Leave.—It has been agreed between the health departments and the service departments, in consultation with the representatives of the medical profession, to allow under certain circumstances service personnel on leave and those temporarily away from their units to use the National Health Service for treatment after April 1. Formerly they were debarred from free treatment by general practitioners under the National Health Service. Service men and women who are living temporarily away from barracks or other service establishments and are more than 2 miles from the nearest service hospital or medical unit can now seek medical treatment from civilian physicians within the framework of the National Health Service as temporary residents, just as a civilian may do when away from home. When service personnel are away for over three months from service medical facilities, it may be necessary for civilian physicians to accept them on their permanent free patient lists. When they are accepted by such physicians for treatment they are entitled to receive drugs and appliances free. They will pay 14 cents per prescription like the general public, but they will be able to reclaim this from their service medical unit. It has also been agreed that, if under certain circumstances drugs and appliances are not obtained at service medical units, they may be obtained through civilian physicians under contract with the National Health Service. For this purpose special prescription forms will be issued and will be recognized by chemists dispensing under the National Health Service. General practitioners treating service personnel under the National Health Service will be paid 74 cents if the patient attends the office, $1.40 for a day visit, and $2.10 for a night visit. In addition, the practitioner will be able to claim 14 cents a mile each way in excess of 2 miles for his automobile.

Needle Broken During Injection.—A Scottish Court of Session has ordered a retrial of a case in which a Scottish woman sued a physician for damages because he left a broken needle in her body (*Scotsman*, Feb. 5, 1955). At the original trial the woman stated that the physician negligently allowed a needle to break when giving her an injection and that the needle was never recovered in spite of several operations. The patient's counsel argued that the needle used was not strong enough and that the physician should have known this. The plaintiff sued for $7,000 damages. For the physician's defense it was not denied that the needle broke and it was claimed that the correct type of needle was used. It broke on withdrawal, an accident that was not uncommon and reflected no lack of care or skill on the part of the operator. The jury rejected the patient's claim and found the physician not guilty of negligence. The patient appealed against the court's findings, claiming that the judge had misdirected the jury. The judge had stated to the jury in

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his summing up that for the claim to succeed there must be such a departure from the normal and usual medical practice as could reasonably be described as gross negligence. The Court of Session has held that the judge's direction did not accurately describe the legal criterion for liability, that therefore the jury's verdict was void, necessitating another trial, that, in order to prove negligence, whether by a physician or anyone else, it was essential to prove a breach of the duty to take the care that the law required, and that lack of care amounting to negligence will vary with the circumstances. Where the conduct of a professional man is concerned the circumstances are not so clear-cut as in most cases seen in the courts. There is ample opportunity for difference of medical opinion in diagnosis and treatment, and a man is not necessarily negligent because he differs from his professional brethren or because he exhibits less skill and knowledge than others might have done. The true test of negligence in diagnosis or treatment is whether the physician is proved guilty of such failure as no physician of ordinary skill would be guilty of if acting with ordinary care.

Health of Young Children in Britain.—In the last 10 years there have been several child health surveys. The latest survey was carried out under the auspices of the University of London, the Society of Medical Officers of Health, and the Population Investigation Committee. This nationwide survey was based on a study of 5,386 children born in the first week of March, 1946, and is to continue until the children are 12 years old. The present report gives the findings relating to the first five years of life of these children. Some confirm what would be expected, namely, that low social class, high parity of the mother, and premature birth have a detrimental influence on the health of young children. Families of four or more children become progressively fewer in passing from the lowest to the highest social group. The children born later into the family tend to be heavier at birth than those born earlier, but by the age of 2 years they weigh less and are shorter and continue to be so up to the age of 4 years. A comparatively high proportion of underweight children are the later born members of large families. Parents belonging to the lower social groups thus produce a greater number of stunted and underweight children and fewer well-developed ones than those of the upper social groups. The reasons for this are not obvious, but undoubtedly nutritional and possibly genetic factors play a part.

Children in large families and lower social groups suffer more from infectious illnesses early in life. The most important factor here is overcrowding. Thus respiratory infections in the children of manual workers are 1.5 times as frequent in houses with two or more persons to a room as in those with one person to one or more rooms. This is borne out by the greater admission rate for respiratory infections in hospitals in Scotland, where there is more overcrowding than in England. On an average, by the age of 5 years 20% of children have been admitted to hospital at least once; later-born children are admitted more often than first-born. The accident rate is not affected by social class or by the size of the family, although it would be expected that accidents would be more likely to occur in poor homes and in large families, with consequent overcrowding and less individual care for each child.

About a quarter of the mothers in the families covered by the survey are working outside the home. This provides an opportunity to study the opposing influences of increased family income and diminished maternal care. There is no evidence that the health of the children of mothers who work outside the home is in any way inferior to that of mothers who stay at home. There is a greater incidence of infection in the very young children of mothers in the first group, but this may be due to crowding in day nurseries. The psychological trauma, if any, produced by early separation of mother and child when the mother goes to work was not investigated. The survey has confirmed the general impression that it is the most careful and conscientious mothers, and those who need advice least, who use the child welfare clinics, rather than the mothers of large families. In all social strata it is the first-born who is taken more frequently to the clinic; the children of large families are less likely to be taken. The latter do not get regular medical supervision until they reach school age. There may be good reasons for this. The mother of a large family has less time to spare to take her children to clinics, and she may believe that experience has made her competent to deal with the younger members of the family herself. It may be that with increase in the size of the family less care is given to the youngest. The fact that 80% of the first-born and only 50% of the youngest children of large families had been immunized against diphtheria suggests that less care is given to the children of large families. The survey showed that 11% of the mothers gave their children fair or poor care, and they were in the poorest and most overcrowded families with many children.

Clinical Trials on Children.—Mr. T. S. Swingler, Member of Parliament, told the House that newborn babies at Bristol Maternity Hospital were given penicillin, not because they needed it but merely as an experiment. He said that some people allowed their enthusiasm for science to override all moral considerations, and he asked the Minister of Health whether he would make sure that, before further clinical experiments on children were undertaken, the nature of such experiments be reported to his department, so that his medical staff could see that there were adequate safeguards against harmful effects. Mr. Swingler further asked whether the Minister would direct hospital management committees on the ethical principles that should govern the conduct of clinical experiments, with particular reference to the importance of securing the consent of the patient or his legal guardian. The Minister, refusing to ban these experiments on children, said that, if a child of his of any age were in hospital and he was told by people of standing that they were interested in knowing the effects of a perfectly safe clinical investigation and, if it might be that they could learn more and drive still lower the infant mortality in this country, he would be delighted to give his consent. He added that the experiments at Bristol were made under the supervision of the professor of medicine and child health, who had declared them to be perfectly safe.

Other members of Parliament disagreed with the Minister and asked for a directive, but he refused to interfere in what was essentially a matter of professional ethics. Mr. Swingler then urged him to ask the British Medical Association and the Medical Research Council to issue a code of ethics. The Minister replied that he might informally draw the attention of these bodies to the matter if he found it necessary, but both the Minister and members of Parliament were agreed that parents should give their consent to clinical trials on children. One member objected that in the Bristol case this was not obtained, and the Minister agreed that this should have been done.

Report on Britain's Health.—The Registrar General's Report on Britain's Health in 1951 (Registrar General's Statistical Review of England and Wales for 1951, London, Her Majesty's Stationery Office, 1955) shows that by 1951 the birth rate had settled to a level above that in the economic depression of the 1930's. There were 1,060 boys born to every 1,000 girls. The decline in infant mortality and the increase in male survival has resulted in a steady rise in the proportion of men to women over the last 30 years. An increase in the marriage rate resulted, the proportion of married women in the age group 15 to 19 years being 83% above the corresponding figure for 1938. Women are not only more likely to marry now but also they tend to marry younger. The influenza epidemic, which was worst in northern England, accounted for a number of deaths. The disease was so widespread that 647,000 sickness claims were made to the Ministry of National Insurance giving influenza as the cause of absence. This was in a working population of about 22 million people. Deaths from influenza were 8% above those from this cause in 1950. Liverpool had its highest weekly death roll since the cholera epidemic of 1849. The steady fall in mortality, which has been going on since the end of the war, received a check. Infant mortality (30 deaths per 1,000 live births) was the same as in 1950.

In 1951 the number of cases of dysentery, whooping cough, and measles was exceptionally high, but poliomyelitis and diphtheria showed a decline. Food poisoning was reported most often in rural districts and in the larger cities. Except for people over 65 years of age, death rates from tuberculosis fell precipitously; yet the number of reported cases, particularly in the age group

15 to 25 years, were higher than before the war. Some of this increase is accounted for by the large number of minimal tuberculous chest lesions found by miniature mass radiography, as well as by more intensive case finding resulting from the careful follow-up of contacts with tuberculous patients. The mortality and morbidity from tuberculosis in Newcastle, Liverpool, and in the industrial cities of the West Midlands and Wales is still excessive. Bronchitis and cancer of the lungs are more common in Liverpool and the West Midlands, while coronary thrombosis and hypertension are, in general, commoner causes of death in urban than in rural districts. Coronary disease and cancer of the lung continue to rise alarmingly. Cancer of the prostate has declined in men below the age of 64, but for other types of cancer death rates by age groups show little change, except cancer of the breast, the mortality from which shows an increase. Death rates from cancer of the uterus have ceased to fall. The death rate from leukemia among children shows a rise, probably because of improved and hence more frequent diagnosis. It is disquieting to find a rise in the mortality in children under 5 years of age from the accidental swallowing of potentially toxic drugs.

Supplementary Estimates for National Health Service.—This year, for the first time since 1949, the government has asked for a supplementary estimate from the Treasury to meet the ordinary expenses of the National Health Service. For England and Wales a further $13,574,400 was asked, and $3,452,400 for Scotland. This sum is to eke out the original estimate of $1,212,400,000 for the current fiscal year. The supplementary estimates would have been larger but for the expected savings of $8,400,000 scattered in small sums under many subheadings. The greatest of these expected savings is $3,385,200 on the hospitals and $1,906,800 on civil defense. The extra expenditure is required mostly for salaries of hospital personnel and for the increased price of goods. There has also been a rise in the cost of the pharmaceutical and dental services. The pharmaceutical services in the whole country account for a further $6,672,400 and the dental services a further $5,322,800. The rise in the cost of the pharmaceutical services is attributed to an increase in the number and average cost of prescriptions, though in England and Wales this has been partly offset by the revised arrangements for pricing prescriptions and paying pharmacists. The rise in the cost of the dental services is due to an increasing demand for dental treatment in Britain (Supplementary Estimates, Civil Estimates, and Estimates for Revenue Department, London, Her Majesty's Stationery Office).

Specialists and the Health Service.—At a meeting of the Joint Consultants Committee, held at the Royal College of Physicians in January, concern was expressed over the lack of balance between the number of posts open to specialists and the number of residents in training. There appears to be a need for improved planning of the specialist services of the country. One of the pressing needs is for suitable quarters for married residents. The committee stressed the desirability of extending arrangements for the consultant domiciliary service, whereby the patient can be seen by a specialist in his or her own home free under the Health Service, to patients in private hospitals. The attention of the Ministry of Health was drawn to the hardship inflicted on patients of modest means who entered such hospitals for domestic reasons or because of lack of adequate accommodation in hospitals under the Health Service and were thereby deprived of the benefit of free specialist advice. Although the Ministry is considering this proposal, its first reaction was that the obligation to provide a domiciliary specialist service is specifically limited to the patient's home.

Cost of Health Services.—It is estimated that in 1955-1956 an extra $67,631,000 will be spent on the Health Service in Britain, making a total annual expenditure of $1,506,286,400, compared with $1,432,865,837 for the previous year (Civil Estimates for the Year Ending March 31, 1956, London, Her Majesty's Stationery Office). Estimated expenditure under most divisions shows an increase. These estimates make no provision for the hospital building program announced earlier this year, expenditure on which is expected to amount to 21 million dollars in 1957-1958. Payments to general practitioners will amount to only 154 million dollars of the 1.5 billion dollar total, or about 10%. Part of the cost of the Service will be offset by patients' payments of 14 cents per prescription. The gross cost of dental treatment (100 million dollars) is below the peak it reached in the early years of the service. The cost of the pharmaceutical service is 154 million dollars. The rise in the estimated cost reflects a bigger demand by the public for the Health Service rather than a rise in the cost of providing the service. The increased payments to hospitals are largely accounted for by higher salaries and maintenance. A recent increase in the salaries of nurses accounts for another 11,200,000 dollars a year. As there are 8,000 more nurses than a year ago, this will also increase the expenditure on the nursing services.

FINLAND

Thrombosis of the Lower Limbs.—On the initiative of *Nordisk medicin* several physicians in Denmark, Finland, Norway, and Sweden have pooled their experiences with thrombosis of the lower limbs. Dr. Otto Wegelius of Helsinki in the May 12 issue states that heart disease is a common precursor of thrombosis, for it was present in 79 of 178 such cases. Other diseases frequently associated with thrombosis and presumably favoring it are polycythemia vera, hypochromic anemia, pernicious anemia undergoing a remission, lymphocytic leukemia, myelocytic leukemia, thromboangiitis obliterans, infectious diseases, and malignant tumors. With regard to the last named, Wegelius recalls that thrombosis in one leg may be the first manifestation of malignant disease elsewhere in the body. At the Maria Hospital, prothrombin determinations of the blood have been made according to two methods, Lehmann's modification of Quick's method being used up to 1951 and Owren's method thereafter. The latter seems to give the better results, for with the Lehmann-Quick method applied to Dicumarol treatment in 122 patients, the embolism frequency among the survivors was 5.7% and the mortality 1.6%. The corresponding percentages for the 108 patients examined by the Owren method were 0 and 1.8 respectively. With regard to the optimal dose of Dicumarol, Wegelius found that it varies with each patient but that, as soon as it has been determined, the prothrombin percentage need be controlled only once or twice a week.

Zilliacus, also of Helsinki, reports a thrombosis rate of less than 1% in more than 8,000 maternity cases yearly. He has learned to dread thromboses when gestation is complicated by myoma or a toxicosis of pregnancy. The patient with myoma for whom cesarean section is indicated appears to be particularly prone to thrombosis. In most cases characterized by obstetric thromboses the thromboses are small and limited to the pelvis. Their existence is suspected when confinement is followed by several days of a rapid pulse and subfebrile temperature resistant to all forms of treatment with the exception of anticoagulants.

Chlorosis.—In *Nordisk medicin* for April, 1955, Brummer and Levanto report five patients with chlorosis treated in the course of three months. It is almost with an apologetic air that so demoded an ailment is discussed in a medical publication. The authors explain the apparent rarity of chlorosis by assuming that many of the patients formerly given this diagnosis are now considered to have pulmonary tuberculosis, bacterial endocarditis, rheumatic fever, and the like. They regard chlorosis not as a disease in a class by itself but as an essential hypochromic anemia of puberty, a contributory factor being an increased need for iron at this age. The healthier lives led by the present generation may partly account for the rarity of chlorosis in modern times.

Prevention and Treatment of Cholelithiasis.—Internists have been inclined to regard the treatment of cholelithiasis almost exclusively as a surgical matter according to Erik Adlercreutz in *Nordisk medicin* for May 12, 1955. Early recognition, however, may lead to effective prevention. With this object in mind the author has scrutinized the records of 192 patients with cholecystitis (163 women and 29 men) treated in his private

practice. The records showed that the cholelithiasis had in many patients been preceded by certain conditions or diseases that are forerunners of gallstones. Among his 163 female patients there was a history of gynecologic diseases in 90, of infections of the urinary tract in 85, of periocular hyperpigmentation in 90, of headache in 93, of rheumatic pains in the neck, right shoulder, and arm in 58, of dyspepsia in 125, and of heart disease in 45. In 10 patients as many as 6 of these forerunners of cholelithiasis figured in the same records, but in 75 the number of forerunners was 3 or less.

ISRAEL

Iron Deficiency Anemia.—At the 18th meeting of the Israel Medical Association several papers dealt with iron deficiency anemia. De Vries and Izak reported that they estimated the hemosiderin content in sections of bone marrow obtained by aspiration biopsy from 8 normal control patients and 39 patients with various hematological disorders. In hypochromic anemia due to iron deficiency the hemosiderin content was low, but in macrocytic anemia with normal mean corpuscular hemoglobin concentration and in hemolytic anemia it was excessive. Hemosiderin must be considered as a dynamic form of stored iron, readily releasing iron when required for the production of hemoglobin. Even in severe iron deficiency anemia small amounts of hemosiderin may be present in the bone marrow. In iron deficiency anemia iron may be deposited in the bone marrow as hemosiderin following iron administration before the hypochromia is corrected. When iron is being utilized for hemoglobin production, a marked drop in bone marrow hemosiderin can be demonstrated within 24 hours. Excessive amounts of bone marrow hemosiderin may be associated with abnormal amounts of iron in the body.

Y. Matoth and M. Aschner reported a series of 168 children with anemia of which 94 cases were due to iron deficiency. Iron deficiency anemia constituted 69% of all cases of anemia, excluding hemolytic disease of the newborn, in the age group from birth to 3 years. Undernutrition was prominent among etiological factors contributing to the production of iron deficiency anemia. Sixty-eight per cent of patients with iron deficiency weighed 30% or more below the average for their age; 65% gave definite histories of diets deficient in iron, whereas in 41% a history of recurrent infection, chiefly diarrhea, was obtained. The percentage of children born to mothers who had had six or more previous deliveries was 27 and that of premature infants and twins was 22.5. Response to ferrous sulfate given orally was good in 64 of 67 patients in whom the follow-up period was sufficient for the evaluation of the results of treatment. The average daily rise in hemoglobin was 0.25 gm. per 100 ml. Although deficiencies in several nutritional factors were present in the examined group of undernourished children, the iron deficiency accounted for the anemia.

Changes of Serum Total Lipids.—Cases of myocardial infarction or other manifestations of atherosclerosis are rare among Jews of Yemenite origin who form about 6% of Israel's population. Dreyfuss reported two patients with myocardial infarction among Yemenite Jews but noted that one of the patients had lived in Israel for 35 years and the second for 21 years. Among the 650 patients with myocardial infarction admitted to the Beilinson Hospital in the period 1936 to 1954, none were of Yemenite origin, according to a review of M. Toor and his coworkers reported in the *Bulletin of the Research Council of Israel* (**4**:202, 1954). One Yemenite Jew admitted to the Beilinson Hospital, however, did suffer from generalized atherosclerosis. This patient had been living in Israel for 38 years. Accepting the general idea that a direct relation between the concentration of the serum cholesterol and the development of atherosclerosis may exist, the authors determined the values of serum cholesterol, total serum lipids, and phospholipids in two groups of Yemenite Jews: 75 who had lived in Israel for 20 years or more (old immigrants), and 192 who came to the country 3 to 5 years ago (new immigrants). In each age group for both men and women the level of total lipids, total cholesterol, and phospholipids was higher in the old immigrants.

Brunner and his co-workers examined four groups, each consisting of 50 normal men in the age group of 35 to 60 years (*Harefuah* **48**:4, 1955). The four groups were: Ashkenazi Jews; Yemenite Jews living in the country more than 30 years; Yemenite Jews living in Israel 4 years and less; and Arabs. The authors also presume that the morbidity and mortality of myocardial infarction and arteriosclerotic vascular disease among Ashkenazi Jews in Israel is similar to that of the general population of the Western world; however, myocardial infarctions are rare among Jews from Moslem countries and almost never are found among Yemenite Jews. The cholesterol levels as well as the phospholipid ratios were particularly low in recent immigrants from Yemen. The Yemenites living in Israel for more than four years had statistically significant increases in cholesterol values but no change in their phospholipid levels. Thus, while the cholesterol levels were lower than those of Ashkenazi Jews, the ratios were similar. Both cholesterol and phospholipid levels were about equal in both the Arabs and the old Yemenite Jews. The factors responsible for these differences in serum levels may be related to differences in nutritional habits and the increased stress of modern civilized life. The rise in cholesterol levels among Yemenites with lengthening stay in Israel must be considered as a typical reaction of acclimatization.

New Hadassah University Hospital Psychiatry Department.—The first batch of patients have now been received by the department of psychiatry at the Hadassah University Hospital in Jerusalem. According to Prof. Milton Rosenbaum of Cincinnati University, the acting director of the department, the major goal is to produce more psychiatrists familiar with dynamic psychiatry. Professor Rosenbaum has come for a year to guide the establishment of the unit. Once a week there will be conferences with the medical services on psychosomatics and a pediatric session jointly with physicians of the children's wards. A group of psychiatric specialists, some from the Hadassah Medical Organization, have volunteered their help in teaching and guiding the growth of the unit. They complement a full-time staff of three physicians, a psychologist, an occupational therapist, a social worker, and nurses. Professor Rosenbaum stated that the department would have a psychoanalytic orientation.

ITALY

Medical and Surgical Convention.—At the Medical and Surgical Convention in Montecatini in May, Professor Campanacci of the University of Bologna reported on 120 patients in whom a gastric resection was made. The results were excellent in 60% of the patients, satisfactory in 28%, and unsatisfactory in 12%. They were definitely worse in women. Postoperative complications included the dumping syndrome, the dyscrasic-edematigenous syndromes, the hepatobiliary syndromes, and the hematological syndrome. The speaker considered the disappearance of pain in most patients and the reduction in the secretion of hydrochloric acid as favorable signs and a neuroendocrine-vegetative lability, which consisted of hypoadrenal hyposympathicotonus, dysproteinemia, and early or late postprandial syndromes, as an unfavorable sign. He said that the postoperative neurovegetative lability is not a new finding in patients who have undergone resection, but it is the accentuation of a preexisting condition that is characteristic of patients with ulcer. The postprandial syndromes are caused not only by alterations of the glucide, electrolyte, and protein balance but also by a reduction of the reservoir function of the stomach. In view of this, a new therapeutic regimen consisting of a diet that is regulated qualitatively and quantitatively and taken at proper intervals should be used; the foods allowed should not be too fluid, too warm, or too cold; sweets should be avoided; carbohydrates should be restricted; an adequate quantity of fats should be maintained; animal and vegetable proteins should be increased; a constrictive girdle should be worn; and the habit of lying down after a meal to avoid the onset of those postprandial syndromes that are mainly of a mechanical nature (dumping syndrome) should be practiced. It is therefore necessary to control the eventual depletion of amino acids, iron,

digestive enzymes, vitamins, hormones, and especially of desoxycorticosterone acetate, cortisone, gastric mucosa derivatives, calcium, and vitamin B_{12}.

Professor Forni and his co-workers reviewed the results obtained in 1,000 patients. Gastroduodenal resection aims at removing the ulcerative lesion and decreasing the gastric secretion of hydrochloric acid. The removal of the lesion is achieved in all the patients, but hypochlorhydria is achieved in only 50 to 60%. The speaker's results were mediocre or poor in 15%. The best results are obtained in gastric ulcers (93.8%) and duodenal ulcers (81.5%) in men; the results are less satisfactory in women. Good results are also obtained in patients with ulcers complicated by stenosis, hemorrhage, and perforations. Success is more easily attained in middle-aged and aged patients and is less common in patients under 20. The best results are observed in those patients whose preoperative hyperchlorhydria was due to a histaminic stimulus. The absolute indication for resection is a duodenal ulcer that is accompanied by a complication or by a syndrome resistant to all medical treatment. A relative indication is the patient's age. Contraindications are a complicated ulcer in a young patient, a constitutional state of anxiety, and tuberculosis.

SWEDEN

Barbiturate Poisoning.—Profound changes have taken place in the treatment of barbiturate poisoning in recent years. Dr. B. Herner in *Nordisk medicin* for May 5 reports 118 patients with acute barbiturate poisoning who were treated during the period 1950 to 1954. Twenty were so serious that the patients were unconscious for more than 24 hours, but only four died. Much of the credit for this high recovery rate goes to the prevention of infections by antibiotics, the prevention of shock by the parenteral administration of fluids, blood transfusions, oxygen inhalation, and keeping the respiratory passages clear. Another factor seems to be the modern switchover from long-acting to rapidly acting barbiturates. Herner urges his colleagues to promote this trend, and he looks forward to the time when the soporifics most in use will be derived from the antihistamine group instead of the barbiturate group. Wisborg and Schuback in *Svenska läkartidningen* for May 6 report 239 patients with barbiturate poisoning in the period 1945 to 1954. In the first half of this period such patients constituted only 0.4% of all the admissions, whereas the corresponding figure for the second half of this period was 1.5%. The cause of death in the 13 who died was bronchopneumonia in 6, heart failure in 5, pulmonary embolism in one, and uremia in one. The authors condemn the use of long-acting barbiturates, the slow excretion of which is one cause of death in these patients. While the men were outnumbered by the women in the ratio of 1:1.69, the mortality rate for men was only 4.3%, whereas that for women was 6.1%. The distribution of these 239 cases by months was surprisingly even, but May was the worst month, and the summer was worse than the winter.

Chlorpromazine in Psychiatry.—Dr. O. Hagnell and his co-workers in *Nordisk medicin* for May 5 reported 130 psychotic patients of recent and of long standing who were given 50 to 100 mg. of chlorpromazine three times a day. A total of between 2 and 5 gm. were given by injection followed by a total of between 5 and 10 gm. by mouth. The authors concluded that this treatment should not be considered ineffective till it has been tried for at least six weks. They have observed several severe complications, which in two patients consisted of great anxiety, promptly ceasing when the drug was withheld. In 3 patients there was evidence of serious damage to the liver, and in 68 the sedimentation rate increased more than 10 mm. per hour during the treatment. In spite of these complications this treatment evidently deserves further trial provided careful laboratory control is assured. In the same issue Dr. S. Cronqvist and his co-workers reported 54 patients with psychoneurosis who were treated with the same drug. This treatment began with injections of 25 mg. three times daily, the dosage being increased during the following few days according to the reaction of each patient. The results were characterized as very good in 21 patients who suffered mainly from tension, restlessness, and anxiety. A patient who had suffered for nine months from a permanent state of terror after a mental trauma was cured after only a few days of this treatment, without any signs of relapse after it was discontinued, but as a rule the improvement could be maintained only by continuous treatment. Because of the fairly high incidence of such complications as jaundice, urticaria, and angioneurotic edema, the authors insist that the indications for chlorpromazine treatment should be carefully considered and the patients informed of the risks before it is attempted.

SWITZERLAND

Annual Meeting of the Swiss Society of Internal Medicine.—At the meeting of the Swiss Society of Internal Medicine in Geneva in May Professor Gsell of Basel stressed the prophylactic administration of antibiotics for acute articular rheumatism. When deciding on the administration of an antibiotic the physician must ask himself: 1. Is the antibiotic absolutely necessary in the treatment of this patient? 2. Which one is indicated? 3. How long and in what doses should it be administered? 4. Does the antibiotic threaten to influence the body's defense reactions, such as in scarlet fever, leptospirosis, or salmonellosis? 5. Is the development of resistant organisms to be expected? 6. Can the antibiotic produce toxic side-effects? Prof. G. Bickel of Geneva stated that side-effects produced by antibiotics may be caused by the inherent toxicity of the products used, by sensitivity reactions on the part of the patient, or by a biological effect secondary to the action of the antibiotic on the microorganisms.

Professor Sheehan of Liverpool described the characteristics of the pituitary insufficiency (not anorexia nervosa) that depends on destruction of the anterior lobe by ischemic necrosis during childbirth. He is opposed to the classic description of hypopituitary cachexia, which he claims is an imaginary disease. If a woman has significant cachexia, it is highly probable that her pituitary gland is entirely normal. True pituitary insufficiency is characterized by a normal nutritive state; the breasts have a normal contour and there is no loss of hair from the head, although pubic hair is affected. These women are pale and pigmentation of the areola papillaris is lacking. The symptoms of hypopituitarism resemble those of myxedema in some respects: decreased basal metabolic rate, sensitivity to cold, almost total absence of sweating, marked mental torpor, puffiness of the face, and anemia. The administration of thyroid produces an effect only on the basal metabolism, but the addition of cortisone makes the other symptoms disappear. The results obtained with cortisone therapy seem to indicate that many symptoms usually attributed to thyroid insufficiency are really due to adrenal insufficiency. The pallor of these patients is explained by atrophy of the antehypophysis, which is unable to secrete intermedin.

Professor Luft of Stockholm reported on the endocrine deficiencies following hypophysectomy, which he performs for the treatment of cancer of the breast, prostate, and certain types of diabetes and hypertension. Two or three weeks after operation thyroid function is rapidly decreased and there is a fall in urinary elimination of the 17-ketosteroids and the corticoids. Some atrophy of the genitals is noted, but there is no cachexia. These deficiencies can be compensated for by the combined administration of cortisone and thyroid extract.

Professor Loeffler of Zurich stated that anorexia nervosa manifests itself by a loss of weight that occurs mostly in women and is due to insufficient alimentation because of an obstinate refusal to eat. In young girls it is the manifestation of an unconscious desire to gain attention. Some of these patients eat secretly and refuse all food in public. It is amazing that the patients are not shocked by their frightening appearance. On the contrary, they find themselves interesting and attractive. When anorexia follows a pregnancy complicated by hyperemesis, it is difficult to make a differential diagnosis from Sheehan's syndrome. Hormone therapy has no effect, except insofar as it exercises an embryonic psychotherapeutic action. The disease is properly treated by psychotherapy.

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GOVERNMENT SERVICES

AIR FORCE

Surgeon General Honored.—During the convocation ceremony of the American College of Chest Physicians, held in Atlantic City on June 4, the surgeon general of the U. S. Air Force, Major Gen. Dan C. Ogle, was presented with an honorary fellowship in the college, and on June 12 at Eureka, Ill., during the centennial commencement of Eureka College, he was given a centennial citation for outstanding achievement. He graduated from Eureka College prior to attending the medical school of the University of Illinois.

Personal.—Brig. Gen. Otis O. Benson Jr., a flight surgeon with the U. S. Air Force Medical Service, on June 6 received an honorary degree of doctor of science from the faculty of Montana State University. This distinction was accorded him in recognition of his being one of this country's leaders in the advancement of aeronautics through medical research.

NAVY

Symposium at New Hospital on Guam.—The naval hospital on Guam, June 21-23, successfully completed the first medico-military symposium conducted by the Navy outside the continental limits of the United States. Capt. Herman A. Gross, commanding officer of the naval hospital, was chairman and host for the meeting of military and civilian doctors from the Marianas, Okinawa, the Trust Territories, Japan, and the Philippines. Rear Adm. F. C. Greaves, M.C., district medical officer, represented the surgeon general of the Navy. The Hon. Ford Q. Elvidge, governor of Guam, welcomed the guests to the island. The consultants for the symposium were Drs. Winchell M. Craig, professor of neurosurgery at the Mayo Clinic, Rochester, Minn.; Bruce Anderson, director of anesthesia, Samuel Merritt Hospital, Oakland, Calif.; T. Eric Reynolds, former surgical consultant to Admiral Halsey; Gerald Gray, plastic surgeon, Oakland, Calif.; Edwin Bannick, Seattle; William Rogers, clinical professor of surgery, Stanford University School of Medicine, Stanford-San Francisco; Walter Work, otolaryngologist consultant at Letterman Army Hospital, San Francisco; Harry Walker, former chief of orthopedic service, U. S. Naval Hospital, Oakland, Calif.; and Capt. W. Van Zile, D.C., chief of dental service, and Commander Leonard Barber, M.C., radiologist, U. S. Naval Hospital, Oakland, Calif.

New Director of Pathology Institute.—The Department of Defense announces the appointment of Capt. William M. Silliphant, M. C., U. S. N., as the director of the Armed Forces Institute of Pathology, Washington, D. C. The Armed Forces Institute of Pathology serves as the central laboratory of pathology for all the armed services and for the Veterans Administration and on a voluntary basis for the U. S. Public Health Service, the Atomic Energy Commission, and other federal medical agencies. The 54-year-old veteran Navy pathologist succeeds Brig. Gen. Elbert DeCoursey, M. C., U. S. Army, whose tour of duty ends on Aug. 1 and who will become commandant of the Medical Field Service School at Brooke Army Medical Center, San Antonio, Texas. Captain Silliphant, deputy director since 1952, was nominated by the board of governors of the Armed Forces Institute of Pathology, composed of the surgeons general of the Army, Navy, and Air Force. This assignment is normally for four years and rotates in order among the Army, Navy, and Air Force.

Captain Silliphant was commissioned in the Medical Corps of the Navy in 1930. In 1933 he began postgraduate study in pathology at the Naval Medical School and since then he has served as pathologist and laboratory officer at various naval hospitals. Assigned to the Philippine Islands one month before the Japanese began their conquest of those islands, he was captured and interned for 37 months. Returning home after liberation of the Philippines in 1945, he served as chief of medicine and pathologist at the Naval Hospital, Long Beach, Calif., and in 1947 was transferred to the Naval Medical School, Bethesda, Md., where for five years he was director of laboratories, executive officer and consultant to professional division, Bureau of Medicine and Surgery. In 1953, he was sent to the Far East for survey studies on Korean casualties, with particular reference to the influence of body armor on war wounds. Captain Silliphant is a diplomate of the American Board of Pathology. He has contributed articles on bronchogenic carcinoma, eosinophilic granuloma, wound ballistics, and comparative studies of the Kahn and cardiolipin tests for syphilis. For distinguished service while a prisoner of war, the Secretary of the Navy issued him the Navy Letter of Commendation. He was also awarded the Army Distinguished Unit badge, Philippine Defense, 1941-1942; and, from the Philippine government, the ribbons of Philippine Defense, Philippine Liberation, and Philippine Independence.

New Editor Appointed.—Capt. Bennett F. Avery, M. C., has been designated director of the Armed Forces Medical Publication Agency. As director of the agency, Captain Avery will be the editor of the *United States Armed Forces Medical Journal* and the *Medical Technicians Bulletin*. He succeeds Col. Robert J. Benford, U. S. A. F., who has been assigned to duty in the office of Dr. Frank B. Berry, the assistant secretary of defense (health and medical).

Personal.—Rear. Adm. Bartholomew W. Hogan, M. C., surgeon general of the Navy, received the honorary degree of doctor of science from Boston College and Tufts University recently.

PUBLIC HEALTH SERVICE

Dr. Sebrell to Retire from Service.—Assistant Surgeon General William H. Sebrell Jr., who has been director of the National Institutes of Health, will retire on Aug. 1, following 30 years of service. He will be succeeded as director of the National Institutes of Health by Dr. James A. Shannon, presently associate director of the Institutes. Dr. Sebrell has accepted appointment as research consultant to the American Cancer Society and will direct the society's institutional research grants program. Commenting on Dr. Sebrell's retirement, Surgeon General Scheele said: "His directorship has been invaluable in bridging a complex period of transition, not only in our own expanding research program but in medical research the world over. Dr. Sebrell, drawing upon a distinguished background of active research and administration, has been one of the nation's leaders in the new research attack on disease, particularly the chronic diseases, such as heart disease, cancer, and mental illness." Dr. Sebrell has earned a world-wide reputation as a medical scientist, particularly through his studies on the B vitamins. He has also received scientific acclaim for important findings in the dietary cause and treatment of liver disease, the effect of pantothenic acid deficiency on the adrenal glands, the nutritional effects of sulfonamides, and the cause and treatment of blood abnormalities.

Dr. Shannon, the new director, has been associate director since November, 1952. He is also chairman of the service's technical committee on poliomyelitis vaccine. Prior to 1952, he was associate director in charge of research at the National Heart Institute. From 1946 to 1949, he was director of the Squibb Institute for Medical Research. He then came to the Public Health Service as a commissioned officer.

Dr. Shannon is a member of the American Physiological Society, the American Society for Clinical Investigation, the Society for Experimental Biology and Medicine, the Harvey Society, and the National Malaria Society. He is a member of the Alpha Omega Alpha and Sigma Xi professional fraternities.

CORRESPONDENCE

LOCAL INJECTION OF HYDROCORTISONE TERTIARY-BUTYLACETATE IN SKIN LESIONS

To the Editor:—In spite of the efficacy of topical applications of ointments and lotions of corticosteroids in certain common skin conditions, such as infantile eczema, atopic dermatitis, pruritus ani, and mild contact dermatitis, direct intralesional injections are still necessary and practical in treating lesions that do not respond readily to topical applications. In this list are small patches of psoriasis, especially on exposed areas; small patches of discoid lupus erythematosus, still persistent after systemic therapy with chloroquine or chlorochloroquine; keloids; localized myxedema; localized scleroderma; granuloma annulare; and small areas of leukemic lesions or other specific cutaneous lesions of the lymphomas. A second group of lesions for which injections may be used includes those that may respond in part to topical applications, especially small areas of the deep lesions of localized neurodermatitis.

We have used suspensions of hydrocortisone acetate and alcohol with an ordinary syringe and needle, also in the cartridge type of syringe (Goldman, L., and others: *A. M. A. Arch. Dermat.* **71**:157 [Feb.] 1955), and with Hypospray jet injection apparatus. Noting the good and persistent response of hydrocortisone tertiary-butylacetate in intra-articular injections by J. L. Hollander (*Ann. New York Acad. Sci.* **61**:512 [May 27] 1955), this suspension has been used by us routinely, in both clinical and investigative studies, for the last past five months. Fifty-eight injections have been given, varying volume from 0.1 to 0.3 cc. (25 mg. per cubic centimeter). The suspension is easier to inject than the suspension of hydrocortisone acetate. A 27 gauge needle may be used for facial lesions and a 25 gauge needle elsewhere. The material appears to be as effective locally as the hydrocortisone. The same essential histopathological changes have been found in the skin of man as have been found with hydrocortisone and its other analogs. Histochemical studies also show the same changes in the tissue (Goldman, L.: *Ann. New York Acad. Sci.* **61**:520 [May 27] 1955). The crystals may persist in site for at least five to six months. This fact must be considered when local injection therapy is used.

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ADENOIDECTOMY

To the Editor:—May I reply to Dr. R. T. Barton's protest (THE JOURNAL, June 11, page 505) of my statement that "deafness, recurring otitis media, and mastoiditis are rarely improved by adenoidectomy," a quotation taken from an abstract in THE JOURNAL Dec. 11, 1954, page 1461. In disagreeing with the above statement, Dr. Barton is undoubtedly voicing an opinion generally held; however, my article and THE JOURNAL's abstract of it would have served little purpose if they had not mentioned the fallacies of the prevailing belief. Many outstanding men believe that progressive deafness, recurring otitis media, and mastoiditis usually are caused by chronic sinusitis and that adenoidectomy not only fails to improve these conditions but may predispose to them. In the original article (Harmful Sequelae of Adenoidectomy in Children with Chronic Sinusitis, *Arch. Pediat.* **71**:233, 1954) there are 64 references and many quotations regarding the protective value of adenoids against the purulent secretions of sinusitis in the production of the above conditions by sinusitis. Those quoted include H. B. Lemere, T. B. Layton, A. D. Kaiser, G. B. McAuliffe, E. C. Marantz, J. A. Glover, J. Wilson, M. M. Cullom, H. M. Taylor, G. E. Martin, J. Crooks, and A. G. Signy.

The adenoid protects not only the upper but also the lower respiratory tract. Kaiser's controlled study, now a classic, has shown that removal of tonsils and adenoids increases the likelihood of lower respiratory tract symptoms. As my article states, these complications are seen only in children with sinusitis whose protective barrier, the adenoids, has been removed. It seems neither fair nor open-minded for one to protest a statement appearing in an abstract when he has not read the original article to determine how the conclusion was derived.

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IODIDE AND ASTHMA

To the Editor:—The Correspondence article by Dr. Leon Unger entitled "Orders for Patients with Asthma," which appeared in the June 11, 1955, issue of THE JOURNAL, page 505, was excellent. I would, however, like to make a correction and an addition. Under direction 7, for severe cases, Dr. Unger orders potassium iodide drams 5 and parenthetically states it equals 8.86 gm. This is incorrect, as 5 drams equal 300 grains or approximately 20 gm., a difference in his dosages of almost 6 grains per teaspoonful between his dram and metric orders. My preference is to start with the smaller dose, to determine the tolerance of the patient for iodides, as they can at times be very irritating. The list might include sodium iodide, intravenously administered, 15.5 grains (0.97 gm.) in 10 cc. distilled water, which is useful in bronchial asthma due to thick mucus plugs. I have seen status asthmaticus cases dramatically relieved with the expulsion of large amounts of thick mucus by its use. All physicians should be familiar with Dr. Unger's fine article, especially the point on not giving morphine to one in an asthmatic attack.

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THE CADUCEUS

To the Editor:—I realize that THE JOURNAL staff is not responsible for the inaccuracy that appears on page 506 of the issue of June 11, 1955. A notice on that page refers to a new insigne to be worn by medical and dental officers of the Air Force. A serpent is not a caduceus. The caduceus (there is only one) is the winged staff of Mercury, who was the Greek patron god of speed, of messengers, of merchants, of thieves, and others. The snakes entwined about Mercury's staff are represented in the position of coitus, signifying cooperation and fertility. I have never known how the erroneous association of the caduceus with medicine arose, but it persists even now in many areas. As you well know, the American Medical Association long ago corrected this error and adopted as its emblem the staff of Aesculapius, the same as that on the new Air Force medical insigne.

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INSURANCE FORMS

To the Editor:—In our increasingly complex civilization, steps to safeguard the security of our population have very rightly increased progressively. This is reflected by the number of forms for insurance companies that the physician is constantly called on to fill out. Although this is an important and necessary part of his work, it would be made much easier if the insurance companies, instead of submitting single forms to fill out, would submit duplicates so that file copies might be kept. I am sure that no insurance company would fill out any form without having a duplicate form to keep in its own file. I cannot understand why they expect the physician to conduct his practice in such a slipshod manner. I have adopted the policy in my office of not filling out insurance forms unless they are submitted in duplicate. How do other readers feel about this?

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MISCELLANY

THE PATIENT'S STAKE IN ACCREDITATION

Robert S. Myers, M.D., Chicago

Reprinted with permission of the author from the Bulletin of the American College of Surgeons *(July-August).*—ED.

Hospital accreditation is the hallmark of patient safety. It is the official recognition of a hospital's voluntary conformation to desirable standards of adequate patient care. It is a reliable, easily accessible guide for public use in the selection of a hospital. Although accreditation is to the hospital world what sterling is to silver, it is a strange and unknown term to the general public.

There are three main reasons why the public knows so little about the meaning of accreditation. In the first place, patients select doctors rather than hospitals, and their physician's staff appointments usually determine the patient's choice of a hospital. This is a well-deserved tribute to the medical profession, but it does not always lead to the selection of the accredited hospital and an appreciation of its value by the patient.

Secondly, the program of hospital accreditation is a mere infant which attained its growth during a hectic period of depression, wars, and fabulous medical scientific discoveries. That the program did not perish is a tribute to the American College of Surgeons, which conceived it in 1918 and carried it singlehanded through the next 35 years. In 1952 the program of accreditation was transferred to the Joint Commission on Accreditation, which is composed of representatives from the American College of Physicians, the American College of Surgeons, the American Hospital Association, the American Medical Association, and the Canadian Medical Association.

The Joint Commission adopted the standards found to be desirable by the College during its years of administering the program and is now in the process of clarifying, revising and strengthening certain portions of these. Twenty physicians, well-trained in all aspects of patient care, are supplied to the Joint Commission by the parent organizations for inspection visits to hospitals in all parts of the United States and Canada. Of the hospitals in these two countries which have applied for accreditation approximately 3,200 have met the rigid requirements. [There are now 21 physician-surveyors; and as of December 31, 1954, a total of 3,513 hospitals were accredited by the Joint Commission.]

The third and main reason for the lack of public knowledge concerning accreditation is the inherent conservatism of the medical profession and hospitals and their aversion to publicizing their accomplishments. Such reticence is often commendable, but the best interest of the patient has not been served by such unnatural reserve. Every opportunity should have been seized to inform the public of the demonstrated worth of accreditation in guarding the welfare and safety of the patient.

Accreditation is not a device to enrich the coffers of hospitals or the pockets of doctors. Accreditation has cost hospitals an untold amount of money; it has multiplied the work of the medical profession; it exacted approximately $2,000,000 from the Fellows of the American College of Surgeons during the first 35 years; and it now requires half a million dollars each year from the funds of the agencies composing the Joint Commission. All this has been done gladly and for one purpose only the benefit of the patient. Surely these facts are worthy of the telling.

What more should the patient be told about accreditation? It is proper to inform him of the unceasing efforts taken to provide him with a suitable, sanitary physical plant which is adequately protected against fire and explosion hazards. He should be told of the need for proper diagnostic facilities, including x-ray and laboratory departments. Mention should be made of the many instruments required to maintain a surgical department and the equipment necessary to sterilize these instruments and other materials. He should know about the hospital pharmacy, which is often as extensive and expensive as the corner drug store. Few patients will realize that the hospital dietary department often serves more meals daily than many hotels in the community. He will be surprised to learn that special diets must be prepared for the patient with diabetes, heart disease, or intestinal trouble. He does not realize the extensive planning and multiple safeguards necessary to protect the newborn infant. Each such activity is but one facet of the hospital.

There are also the many highly trained people required for the adequate care of the patient—record librarians, nurses, dietitians, x-ray and laboratory technicians, pharmacists, physiotherapists, occupational therapists, social service workers, maintenance men, housekeepers, purchasing agents, maids, orderlies. Hidden below the surface, like the main body of an iceberg, many of these vital personnel are not visible to the patient during his hospital stay, but they are an absolute necessity, and they cost money.

Many uninformed patients who complain about the high cost of hospital care compare hospitals with hotels, which make money with lower daily charges. The public should be told about the costly and unique equipment required by hospitals and the many specialized personnel needed to serve the patient 24 hours a day. The patient doubtless has never thought of the expense involved in guarding his life and health, and it has never occurred to him that such profitable sidelines as liquor sales are not revenue producers for hospitals.

What is required of the medical staff of an accredited hospital? The program of accreditation has conclusively demonstrated that the medical staff of the hospital holds the key to accreditation through a series of self-imposed controls or standards designed to protect the patient. This voluntary effort of the profession to maintain adequate standards of patient care is usually not apparent to the public.

Detailed histories and physical examinations must be made for the protection of the patient. Complete medical records must be dictated promptly, operative notes written and consultations recorded. Radiologists are required for searching diagnostic studies, and every bit of tissue must be examined by the pathologist. Skilled anesthesiologists are required to administer the anesthetic and are expected to follow the patient until he recovers from anesthesia. Such activities of doctors are not haphazard occurrences. They are part of the integrated activities of an organized medical staff found in an accredited hospital.

Little does the patient realize the time and effort demanded of the physician to serve as a member of the five essential medical staff committees required for accreditation of a hospital. The executive committee sets staff policy and provides discipline; the credentials committee assesses the qualifications of physicians and assigns them to privileges and to departments; the joint conference committee consults with the governing board on problems of interest to the board and medical staff; the medical records committee examines countless records, evaluates their contents and assesses the care of the individual patient; the tissue committee reviews every operation and decides the justification for surgery.

In order to inform the medical staff about the quality of patient care so that it may be maintained at the highest level, physicians are required to meet at regular intervals. There are monthly medical staff meetings, weekly or monthly departmental meetings and clinical pathological conferences, to say nothing of the nonrequired but equally educational county, state and national medical meetings and conventions of various specialist societies.

Does the patient know that accreditation requires a competent administration, composed of a trained and experienced administrator and a governing board selected for its knowledge, interest and experience in hospital affairs? To this segment of the hospital falls the grave obligation of assuming moral and legal responsibility for the welfare and safety of the patient in addition to the financing and direction of the hospital.

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[Presented at the Catholic Hospital Association's thirty-ninth annual convention, Atlantic City, New Jersey, May 19, 1954; and, with amendments, reprinted with permission from *Hospital Progress*, August, 1954.]

And, finally, the patient should be told that accreditation places the responsibility for medical ethics squarely on the medical staff and the administration of the hospital. This is vitally important to the patient for adequate control helps protect his health, his life and his pocketbook. Unethical or unprofessional conduct consists of more than unjustified surgery or the unnecessary or unsanctioned removal of normal organs. Fee-splitting and ghost surgery exist in some hospitals, regardless of size, location or religious affiliation. All these evils must be regarded as morally wrong, and it is time for the medical profession and hospitals to close ranks to eliminate those who violate the principles of medical ethics and bring discredit on honest physicians and hospitals.

It is heartening to witness the recent vigorous demands from all segments of the medical profession and from administrators of numerous hospitals for eradication of unethical practices. As long as doctors are human, there will be transgressors among the medical profession, but no other business, trade, occupation or profession contains so many able, dedicated men and women devoted to the betterment of mankind as the medical and hospital professions.

How should the public be informed about the benefits of accreditation? There are several steps worthy of consideration. First, members of the medical profession should demand that all hospitals in which they work gain accreditation, and they should insist that their patients enter only accredited hospitals for treatment. Moreover, the profession, working through local medical societies, should inform the public of the benefits of accreditation by newspaper articles and by talks to lay groups.

Hospitals should supplement this public information program by distributing to patients factual and informative pamphlets concerning the patient's stake in accreditation. This is an era of brand names and accepted products. An intelligent public wants the best, but it cannot be expected to appreciate anything as intangible as accreditation unless it is properly informed. The accredited hospital is a blue ribbon product, and it needs to be publicized.

There have been suggestions from the medical profession and hospitals that accreditation should be made compulsory by local government health agencies which would demand accreditation by the Joint Commission as a requirement for government licensure of a hospital. There is some doubt that such action would be entirely wise. Accreditation has been voluntary from its inception 36 years ago and every effort has been made to avoid even the suggestion of compulsion. The program has been entirely free from discrimination against race, creed and color, and, most important of all, political and other undesirable influences have never affected the decisions of the accrediting agencies.

It is not certain that such integrity could be maintained in any liaison with government. The co-operation among the parent organizations comprising the Joint Commission has been most heartening, and the program of accreditation is being strengthened and expanded. Public demand for accreditation will accomplish the objectives of government action without sacrificing the advantages of integrity and freedom from undesirable influence now enjoyed by the Joint Commission.

Privileges bring responsibilities, and the patient bears certain moral obligations in return for the benefits he receives from accreditation. It is to be expected that he will patronize those hospitals whose physicians and administration have sacrificed time, money and effort to obtain accreditation for his benefit. Moreover, the patient must recognize that the standards of accreditation proscribe surgery and medical treatment in the absence of specific medical indications. The patient's request alone is not a valid indication for specific surgical procedures or medical treatment, and the patient must not demand special consideration in violation of accepted principles of accreditation.

If the medical profession and hospitals believe that their prime concern is the welfare and safety of the public, they are irrevocably committed to the program of accreditation, and it should be their combined objective to educate the public about the benefits of accreditation. Anything less is a betrayal of our medical ideals.

THE LEISURE CORNER

LOOKING AT MODERN ART

Perhaps among no other group of professional persons has an interest in painting and sculpture been more extensively cultivated than among American physicians. Thousands of physicians have translated their interest into action by joining the ranks of Sunday painters, starting modest collections of paintings and sculpture, or avidly attending art exhibitions. While the exact relationship between art and medicine has never been defined to the complete satisfaction of the two types of practitioners, both disciplines have much in common. Capable physicians and artists have a quick eye, possess manual dexterity, entertain a sympathetic interest in their environment, and exhibit a comprehensive understanding of their fellow human beings.

In order to understand contemporary art or, for that matter, the art of any historical period, it is necessary to view art in terms of the society, culture, and era that produced it. Unlike science, there are no absolute standards by which art can be measured, there are no authorities whose judgment can be said to be omniscient, and there is no single, correct way to look at a painting or a piece of sculpture. Although the role of the artist has been variously interpreted at different times, Siegfried Giedion offers this succinct observation: "The artist," he asserts, "in fact, functions a great deal like an inventor or a scientific discoverer: all three seek new relations between man and his world. In the artist's case these relations are emotional instead of practical or cognitive. The creative artist does not want to copy his surroundings, on the one hand, or to make us see them through his eyes, on the other. He is a specialist who shows us in his work as if in a mirror something we have not realized for ourselves: the state of our souls. He finds the outer symbols for the feelings which really possess us but which for us are only chaotic and—therefore—disquieting, obsessive stirrings. This is why we still need artists, however difficult it may be for them to hold their place in the modern world."

While many persons are more accustomed to reading about art in magazines and newspapers, the opportunity to look at a picture, "in the flesh" as it were, would not only develop more sensitive perception but also increase enjoyment. This medium has provided many contemporary artists with a new vocabulary to explain, portray, and interpret the vast numbers of visual and auditory stimuli that bombard 20th century life. Modern art is more concerned with expression than with representation, with creation rather than with imitation. If anything, modern art is characterized by various styles and various techniques, by experiment, by daring, and by lack of conventionality.

Cubism provides one of the most significant developments in modern art. In order to appreciate a cubist painting, a spectator should stop being a passive onlooker; instead, he should make a serious attempt to identify himself with the artist and follow the development of the painting step by step. For example, a cubist painter will start with a known object as his point of departure and attempt to show all sides of it at one time, that is, front, back, sides, inside, top, and bottom. In short, what he tries to do is depict the entire object visually as a single experience.

As can be surmised, cubism permits an artist considerable freedom. Despite the fact that the artist uses a known object as the basis for his work, he will take many liberties while painting, combining aspects that ordinarily escape the spectator's eye. The intent of a cubist painting is neither psychological nor literary; in essence, it provides a new method and a new visual language to extend the possibilities of experience. Since cubist painters are more interested in transforming an object than in transforming a subject, they manipulate their material at will.

Futurism began to interest a number of artists several years after the advent of cubism. This aspect of modern art is concerned with motion. In both cubism and futurism the dissection of form is combined with a constant reassembling process. Ob-

This article is based in part on material drawn from a book written by Katharine Kuh: "Looking At Modern Art," Art Institute of Chicago, 1955.

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jects are disintegrated only to be put together in new combinations, so that complete form and motion are recorded in single visual experiences. A notable difference between cubism and futurism lies in the fact that cubist painters combine all sides of an object simultaneously, while futurist painters attempt to express complete motion at one time. The goal of a futurist painter is not so much to suggest motion—this has been done in the past—but actually to depict and capture motion on canvas or paper. Futurist painters have tried to accomplish this by a series of overlapping forms that illustrate the path of an object as it moves through space. They did not merely want to show a man running—what they wanted to do was to show the running of a man, in fact, the continuous running of a man at a given time. Marcel Duchamp's famous painting "Nude Descending a Staircase," was in one sense a motion-picture technique that anticipated the results of the dissection of motion by the stroboscopic camera.

As employed today by the *cognoscenti* of the modern art world, the term expressionism has more than one meaning, although it chiefly implies emotional expression. In general, an expressionist painter will sacrifice a naturalistic appearance for a completely personal interpretation, producing an emotional feeling of a scene rather than its visual counterpart. This is accomplished by exaggerating color, form, line, and space.

Psychoanalysis has provided some artists with source material for their work. A case in point is surrealism, which is concerned mainly with irrational dream material. In an effort to escape the difficulties and ennui inherent in much daily life, the early surrealist painters claimed that dreams supplied the only reality and it was through dreams that emotions could be released; hence, the name of this particular art movement—sur (super) realism. In surrealism, barriers of time as well as moral judgments are frequently eliminated and the painter arranges a combination of unconscious experiences on a single canvas where the past, the present, and intervening psychological states are superimposed.

The art movement known as Dadaism had a basic philosophy that differed from that of surrealism, which it antedated. Dadaism evolved during the First World War as a protest against war, and it attempted to escape disillusionment by complete negation. The eminent critic, Lewis Mumford, once called Dadaism "an irreverent commentary on the inflated platitudes of politicians," and Clifton Fadiman facetiously referred to the late Gertrude Stein as "the Mamma of Dadaism." On the other hand, modern technology and science have given artists a wealth of new materials and new approaches for using old materials. As a result, contemporary artists have had greater opportunities for experimentation. The mobile, a new kind of sculpture, provides a good example. The development of the mobile can be traced to contemporary interest in motion and the diversified use of materials. Heretofore, most sculpture has been static, occasionally suggesting movement but not participating in movement itself. The mobile, which is based on the idea that its various parts are flexible, is designed for motion. As it moves, the mobile presents numerous relationships to the spectator. Generally, an observer must move around three-dimensional sculpture in order to see it properly. Since mobiles presuppose that both the sculpture and the spectator move, many changing aspects can be seen at one time.

In recent years, a new school of painting that can loosely be described as abstract expressionism has been gaining adherents in the United States and Europe. As in the case of surrealism, abstract expressionism is geared more to the needs of the artist than to the immediate understanding of the general public. Abstract paintings are frequently filled with allover patterns devoid of a beginning or an end. Form is relatively unimportant —mood is what counts. There is apparently no one central idea, no preliminary sketch in a painting classified as abstract expressionism. An abstract composition will provide an artist with an immediate experience in which he depicts what he feels at the moment, and this culminates in completely abstract designs.

For many people contemporary art and sculpture is either a joy or a puzzle. Nonetheless, its influence has been felt in every nook and cranny of American life. If there is any doubt, one need only look at modern furniture, architecture, transportation, and household appliances, to name an important few. Whatever the attitude of artists and spectators may be to certain aspects of modern art, it would be well to keep in mind the point of view that has been expressed by Katharine Kuh. "In our own way of life," she declares, "each man is allowed to express himself independently; each artist can work as he wishes. So also the spectator, sharing this same freedom, is entitled to form his own judgments. No government imposes its will, no one school of art can dictate policy in a field so open to competition. . . . One need only observe the sterility of art under dictatorships like Nazi Germany or Soviet Russia to realize how official directives and censorship obstruct creative expression and enforce uniformity."

MEDICAL FILM REVIEWS

The Magic Touch: 16 mm., color, sound, showing time 9 minutes. Educational Collaborator: Edward G. Johns, Ed.D., Department of Health Education, University of California at Los Angeles. Produced by and procurable on purchase ($90) from Avis Films, Inc., 932 N. LaBrea, Hollywood 38, Calif.

The purpose of this film is to counteract apprehensions in regard to immunization by showing (1) how immunization protects the body against disease and (2) how insignificant the mild discomfort of being immunized is in comparison to the benefits derived. Sally, Jill, and Jerry are members of an elementary school class that is visited by the school nurse preparatory to immunization. The nurse's talk covers the two points described above. Because they understand and appreciate the nurse's message, the children are not apprehensive when they undergo actual immunization, and as a result of their proper attitude they find that the "magic touch" is indeed a slight discomfort. At home, the children play "doctor and nurse," with Sally's doll as patient, to recapitulate and emphasize the lessons they have learned from the school nurse and from their own experiences in being immunized. This is a well-acted film on the need for immunization. Technically, the method of flaming the needle and of using the same needle for successive injections is questionable. The possibility of the spread of infectious hepatitis suggests the use of individual autoclaved needles. In addition, the possibility of the transformation or precipitation of the proteins in the toxoid by heating the small amount left in the needle could produce untoward sensitizations. The use of the public health nurse for classroom teaching varies from community to community. This film is suitable for showing in the classroom and to parent-teacher groups.

A Matter of Time: (Cleared for Television): 16 mm., color, sound, showing time 14 minutes. Produced in 1954 by Unifilms for the Institute of Life Insurance, under the technical guidance of Dr. Francis R. Dieuaide, Director of the Life Insurance Medical Research Fund. Procurable on loan from Association Films, Ridgefield, N. J., and regional libraries of Association Films.

This film shows the laboratories, hospitals, and medical schools where scientists and researchers are seeking a cure for heart disease. Such research developments as the "jiggle-bed," oscillograph, and the mechanical heart are featured, with an explanation of the causes and effects of various forms of heart disease. Animation and scale models are used to illustrate the four types of heart disease: arteriosclerosis, hypertension, rheumatic fever, and congenital malformations. The film also suggests aids to the average person in avoiding heart disease and attaining a longer, healthier life. There are innumerable parts that are not understandable to laymen, particularly the photomicrographs of arterial sections, many unexplained sequences of laboratory devices, and charts. Apparently, the film is designed to impress people with the need to protect their hearts, but this objective has not been reached. The very positive statement, given in at least two instances, that heart diseases will be conquered in time is not particularly reassuring when one knows the relative impossibility of that in the modern classification of disease and the tabulation of causes of death. With a good discussion leader, this film would be suitable for service and hospital groups, heart association workers, and for health education at the college level.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Adams-Stokes Syndrome: The Treatment of Ventricular Asystole, Ventricular Tachycardia and Ventricular Fibrillation Associated with Complete Heart Block. S. R. Robbin, S. Goldfein, M. J. Schwartz and S. Dack. Am. J. Med. **18:**577-590 (April) 1955 [New York].

Four cases of heart block with Stokes-Adams syndrome are described in two men and two women between the ages of 48 and 77 years to illustrate the two different mechanisms that may precipitate the attacks, namely, ventricular asystole and ventricular tachycardia or fibrillation. The approach to management should be individualized, with treatment adjusted according to the underlying mechanism. Epinephrine is the drug of choice for the treatment of ventricular systole and should be given in a sufficient amount with the aid of electrocardiographic control. It is contraindicated when ventricular tachycardia or fibrillation is the mechanism for the attacks. Procaine amide (Pronestyl) and quinidine have been found to be ineffective and even harmful in the treatment of ventricular tachycardia or fibrillation in the presence of heart block, because of their depressant effect on the junctional tissues. Isopropyl arterenol (Isuprel) was given to two of the authors' patients. In one of them the causal mechanism was ventricular systole and in the other, ventricular fibrillation. Isuprel stimulates the higher ventricular centers and, therefore, does not predispose to ventricular fibrillation. It appears to be the drug of choice when the basic mechanism for the Stokes-Adams syndrome is ventricular tachycardia or fibrillation and when ventricular asystole alternates with tachycardia or fibrillation in the same patient. Isuprel is given in doses of 10 to 15 mg. sublingually, four or five times daily for the prevention of attacks. For treatment during attacks the frequency of the administration and the dose must be increased, but this varies in different patients and even in the same patient depending on the patient's tolerance and requirement. One of the authors' patients required 15 mg. of the drug every hour for the first 24 hours to prevent recurrence of the attacks, and in the other patient the optimal dose was 7.5 mg. four times daily. Three of the authors' patients had atrial flutter associated with the atrioventricular block, a rare combination.

The Relation of Subcutaneous Focal Sensitivity to Referred Pain of Cardiac Origin. M. A. Kennard and F. P. Haugen. Anesthesiology **16:**297-311 (May) 1955 [Philadelphia].

The referred pain that usually occurs in the left shoulder and upper arm, but may also occur about the right shoulder and the neck, is recognized as a frequent accompaniment of the precordial distress that results from myocardial insufficiency. In some patients with chronic coronary insufficiency the referred pain becomes the outstanding symptom and the arm and shoulder become rigid and atrophic in consequence of the pain. Marked relief and return of peripheral function may follow procaine injection of trigger areas about the arm and shoulder. During the treatment of patients with cardiac disorders, the authors observed that the abnormally sensitive trigger areas lay in well-defined locations and that the pain from these trigger spots always radiated in the same directions. In order to obtain more information on the trigger sites they searched for them in 72 patients with cardiac disorders, 35 patients with thoracic disorders not related to the heart, and 46 patients with nonthoracic disorders. Firm but gentle pressure of the hand and fingers was applied over the entire chest, back, and shoulders. If a person without signs of cardiac or other disorder presses firmly on certain areas of his chest or back he may find some spots that are more sensitive than others. In these same regions, cardiac patients may be much more sensitive and the pain may be spread over much larger areas so that light pressure alone may cause them to flinch. On firm pressure the pain is discrete, stabbing, and "hot." The pain remains for several minutes after the pressure is removed in the controls. In sensitive cardiac patients this is many times magnified. Both the controls and cardiac patients were completely unaware of these sensitive spots until they were examined. Furthermore, the sensitivity to pressure was not related to their spontaneous chest pain except in a few cases. Of the two spots that were most frequently sensitive, one lies on the chest in the midclavicular line about 1 in. below the clavicle, and the other on the back of the shoulder at the upper border of the trapezius. Next most frequent were those at the anterior axillary border and those in the second and third intercostal spaces on the chest. Pressure over the flat surface of the scapula also frequently produced pain. A severe degree of sensitivity was observed only in patients with cardiac disorders. Furthermore, in these cardiac patients the sensitivity was either entirely or predominantly on the left side. There seemed to be a relationship between the degree of spontaneous pain and degree of sensitivity. Those cardiac patients who had severe coronary pain during their illness demonstrated the greatest tenderness to pressure. In many cardiac patients the tenderness became less as the spontaneous pain diminished during convalescence, but there was no significant correlation between the severity of the trigger pain and the subsequent course of the cardiac disorder. It is suggested that (1) the trigger areas are the result of focal inflammatory changes based on reflex vasomotor processes and that this fact accounts for their persistence when the visceral source of the pain is no longer present; (2) the sensitive areas lie in close relationship to the larger and more superficial nerves; and (3) the syndrome of referred cardiac pain can best be explained by the use of pathways of referral from the visceral autonomic source of excitation to other autonomic afferent fibers from the shoulder and neck, which enter the same ganglia and the same cord segments as do the cardiac afferent fibers. Such a concept of referral from autonomic-to-autonomic, rather than autonomic-to-somatic, would explain many other types of severe deep-lying pain that do not follow the usual segmental somatic patterns.

Quinoline Therapy in Asthma: Report of 500 Cases. C. F. Geschickter. South. M. J. **48:**497-509 (May) 1955 [Birmingham, Ala.].

A series of 500 patients with bronchial asthma was treated with a new quinoline derivative—N, N-diethyl-cis-Δ^4-tetrahydrophthalamic acid (Phthalamaquin). It has both bronchodilator and antihistaminic properties, as well as the unusual advantage of localizing in the respiratory tissues. It is administered either orally or intramuscularly in 50 mg. doses in the form of its organic salt, and intravenously in the form of its ascorbic acid salt in doses of 200 to 500 mg. In long-continued clinical use the safe oral dose is 3 mg. daily per kilogram of body weight. Patients have been treated over periods from 6 to 48 months. The results were good to excellent in 80% of the patients, fair in 10%, and poor in the remaining 10%. All of the patients had previously failed to respond to other treatments.

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Adverse Effects of Therapy in Allergic Disorders. A. Sterling. GP **11:**93-94 (May) 1955 [Kansas City, Mo.].

Many allergic patients who would benefit from desensitization and thus avoid future bronchial asthma and invalidism are lost to the medical profession because of overdosing and subsequent constitutional reactions. Desensitization with potent material should be undertaken cautiously in highly sensitive persons, with frequent minute doses in dilutions as weak as 1:100,000 to 1:200,000 intradermally. It is best to keep new patients in the office for 15 to 20 minutes after injections to make sure shock reactions do not develop in them. The therapeutic need for epinephrine and related compounds varies widely in different persons. Patients may go through a temporary stage in which they are resistant to the effects of epinephrine, and to continue to give the drug in larger and larger doses during this stage can prove extremely harmful to the patient. The antihistamines are valuable, especially in the treatment of hay fever because of their drying effect on the respiratory mucosa. In patients with hay fever, asthma, and bronchitis, however, interference with expectoration may cause discomfort. The sedative effect of these drugs must be kept in mind too. The prolonged use of rectal suppositories may cause pruritus or proctitis. Corticotropin, cortisone, and hydrocortisone block the allergic process but do not aid in diagnosing the cause of the difficulty. Electrolyte metabolism must be checked constantly during therapy with these agents. Potassium iodide liquefies bronchial secretion and may relieve difficult expectoration, but it induces marked rhinitis, which may in turn aggravate the cough syndrome.

The Low Sodium Syndromes. E. G. Margolin and J. P. Merrill. GP **11:**58-69 (May) 1955 [Kansas City, Mo.].

A low sodium syndrome is produced by one of three mechanisms: dilution of sodium, i. e., the retention of water over and above the retention of sodium; depletion of sodium, i. e., an actual decrease in the amount of sodium present in the body, in the presence of essentially normal amounts of body water; and redistribution of sodium or water in the body (phenomenon of adaptation), i. e., the loss of sodium from the extracellular, measurable space or its dilution by water leaving the intracellular space. Differentiation of these three types of hypotonic state is based on the following clinical and laboratory data: the patient's normal weight and recent changes in weight; the presence or absence of edema and dehydration; the recent intake and output of fluid; consumption of food; existence of vomiting, diarrhea, and profuse sweating; the presence of visceral disease such as cardiac failure, hepatic insufficiency, renal impairment, or terminal cancer; and determinations of serum protein, hemoglobin level or hematocrit, carbon dioxide combining power, chloride, potassium, serum nonprotein nitrogen, and sodium in the urine and, sometimes, in other body fluids. The best treatment for a patient with hyponatremia due to dilution is restriction of water, accompanied by general supportive measures. Hyponatremia due to sodium depletion is often the direct result of various therapeutic maneuvers. Sodium replacement therapy is usually indicated, but it must be accompanied by careful checking of the general electrolyte balance, particularly against potassium depletion. Hyponatremia due to redistribution should not be treated by administration of excess salt. It is seen postoperatively or is the result of chronic stress and is an expression of underlying disease. It may be clinically asymptomatic. Specific instances of low sodium syndromes occur in congestive heart failure, cirrhosis with ascites, chronic nephritis, adrenal cortical hypofunction (Addison's disease), acute renal insufficiency, the nephrotic syndrome, and in certain cases of central nervous system disease or severe tuberculosis and other cachectic states.

Euthyroid Patients with Early Eye Signs of Graves' Disease: Their Response to L-Triiodothyronine and Thyrotropin. S. C. Werner. Am. J. Med. **18:**608-612 (April) 1955 [New York].

In a series of 10 patients between the ages of 24 and 63 years with early ocular signs of toxic diffuse goiter consisting of widening of the fissures and a limited degree of proptosis, 7 were euthyroid by every criterion available including basal metabolic rate, fasting cholesterol levels, and chemical serum precipitable iodine values; the other three were euthyroid by all criteria except the serum precipitable iodine, the levels of which were high. After an initial determination of radioactive iodine (I^{131}) uptake at 24 hours by the thyroid made with a 15 μc test dose in the 10 patients, all were given L-triiodothyronine by mouth in doses ranging from 0.07 to 1 mg. daily, for eight days. On the morning of the eighth day the radioactivity in the thyroid was measured, a second 15 μc dose of I^{131} was administered and the 24 hour uptake again determined. The absence of decrease in uptake by the thyroid in these euthyroid patients with ocular signs of toxic diffuse goiter was striking in contrast to the marked decrease in uptake shown by 30 euthyroid control persons. Thyrotropin was administered intramuscularly to eight patients in doses of 10 units (30 mg.) daily for three days. A diagnostic dose of 15 μc of I^{131} was given orally on the third day, and the uptake was determined 24 hours later. Although there was a slight increase in average uptake of I^{131} by the thyroid, the amount was negligible in five of the eight patients tested. A brisk increase in the serum precipitable iodine level followed thyrotropin administration in all patients. The author's patients responded to triiodothyronine and thyrotropin like patients with overt toxic diffuse goiter. It is concluded that these patients did, in fact, have toxic diffuse goiter. It is demonstrated that the normal pituitary-thyroid relation is disrupted in these patients and that euthyroidism can be maintained despite this disruption. The disruption of the normal relations and the abnormal responses of these patients to thyrotropin may be considered as further evidence that toxic diffuse goiter is not caused by hyperpituitarism but is mediated by mechanisms apart from that gland. Triiodothyronine and the 24 hour uptake method provide a new and highly reliable test of thyroid function.

Significance of Lowering of Vitamin E Concentration in Serum of Patients with Liver Diseases. A. Bäumer and R. Beckmann. Klin. Wchnschr. **33:**431-434 (May 1) 1955 (In German) [Berlin, Germany].

The concentration of vitamin E in the serum was determined in 54 patients, 15 of whom had epidemic hepatitis, 8 cirrhosis of the liver, 5 obstructive jaundice, 11 so-called intermittent juvenile jaundice of Meulengracht type, one subacute atrophy of the liver, 2 primary carcinoma of the liver, and 8 carcinoma of various organs not associated with icterus. Results showed that diseases of the liver and jaundice of Meulengracht type are almost always associated with a disturbance of vitamin E metabolism. As a rule this disturbance is manifested by a lowering of the concentration of vitamin E in the serum. A marked increase in the concentration of vitamin E in the serum of one of the patients with carcinoma of the liver not associated with jaundice could not be explained. To study the influence of vitamin E on the function of the adrenal cortex, three patients with cirrhosis of the liver, two with hepatitis, one with cholangitis, and four with jaundice of Meulengracht type were treated with alpha-tocopherol. Concentration of vitamin E in the serum and total-neutral-C-17-ketosteroid excretion in the urine were determined in these patients before and after treatment with alpha-tocopherol. An increase in the total-neutral-C-17-ketosteroid excretion in the urine was observed in all 10 patients. It was associated with increase in concentration of alpha-tocopherol in the serum of these patients and with definite improvement of their subjective general complaints. Vitamin E did not exert any influence on the changes of the metabolism of the biliary pigment and the serum protein structure in the patients with diseases of the liver, and it did not have any effect on the hyperbilirubinemia of the patients with icterus of Meulengracht type.

Clinical Evaluation Studies in Lepromatous Leprosy: First Series: Diasone (Diamidin), 4-4'-Diaminodiphenyl Sulfone, Dihydrostreptomycin. J. A. Doull. Internat. J. Leprosy **22:**377-402 (Oct.-Dec.) 1954 [New Orleans].

A series of patients with lepromatous leprosy were selected and assigned in equal numbers to six therapy groups by a method that gave priority to comparability in sex and age and took into account other characteristics relevant to prognosis. These groups were subjected to impartial appraisal after 32 to 48 weeks. The drugs and combinations used were: (1) diasone

(diamidin), (2) 4-4'-diaminodiphenyl sulfone (DDS), (3) dihydrostreptomycin sulfate, (4) diasone plus dihydrostreptomycin sulfate, (5) dihydrostreptomycin sulfate plus sodium *p*-aminosalicylate and (6) a placebo or sodium *p*-aminosalicylate alone. Therapy and examinations were completed in 852 patients. Diasone, DDS, and dihydrostreptomycin proved of definite and about equal value in the treatment of lepromatous leprosy. A combination of dihydrostreptomycin and diasone showed no advantage over either given singly, and addition of sodium *p*-aminosalicylate to dihydrostreptomycin did not augment its effectiveness. The proportion of patients who, on clinical grounds, were considered to be moderately or markedly improved was 20% after 32 weeks, and 25 to 30% after 48 weeks. Very few of the patients who were given placebos improved, but about 17% of the controls given sodium *p*-aminosalicylate showed improvement, which suggests that this drug may have some beneficial effect.

Type E Botulism Due to Salmon Eggs. C. E. Dolman, G. E. Darby and R. F. Lane. Canad. J. Pub. Health **46:**135-141 (April) 1955 [Toronto, Canada].

In November, 1954, three young Indian women (sisters) in British Columbia fell ill with symptoms suggesting botulism. The incriminated foodstuff was salmon egg cheese, made by a tribal method that involves washing and smoking the mass of eggs, which are then allowed to mature in boxes or tins for two to four weeks before consumption. The sisters ate the salmon egg cheese raw, and one of them died. A strain of Clostridium botulinum type E was isolated from her stomach contents, and also from samples of the salmon eggs consumed. Its toxigenic capacity in laboratory mediums resembled that of other type E strains, cultures attaining a potency of 1,000 to 3,000 mouse minimum lethal dose per milliliter. The circumstances of this outbreak of botulism permitted the lethal dose of type E toxin for man to be fairly accurately determined at around 500,000 mouse minimum lethal dose. In the period 1944 to 1954 there have been four outbreaks of type E botulism in British Columbia, all due to uncooked or insufficiently cooked fish or fish products. Of the nine persons affected, six died.

Recognition of Abnormal Hemoglobin Syndromes. R. H. Alway. Journal-Lancet **75:**215-222 (May) 1955 [Minneapolis].

Filter-paper electrophoresis provides a relatively simple and inexpensive means of determining the electrophoretic mobilities of hemoglobins A (adult), S (sickling), C, and F (Fetal). Hemoglobins D and F may be recognized by further studies. Although sickling is most easily recognized in patients with sickle-cell anemia and sickle-cell thalassemic disease, it is also found in those with sickle trait, sickle-cell hemoglobin C disease, and sickle-cell hemoglobin D disease. Leptocytosis suggests the presence of hemoglobin C. It is most marked in homozygous hemoglobin C disease but is also seen to a lesser extent in sickle-cell hemoglobin C disease, sickle-cell anemia, hemoglobin C trait, and in thalassemia major and minor. Erythrocyte hypochromia and microcytosis may be noted in the thalassemic conditions. Splenomegaly is most marked in thalassemia major. It is progressive in sickle-cell thalassemic disease and sickle-cell hemoglobin C disease but usually regresses before adolescence in sickle-cell anemia. It is less marked in homozygous hemoglobin C disease and thalassemia minor. Arthralgia is noted not only in the three most common forms of sickle-cell disease, i. e., sickle-cell anemia, sickle-cell hemoglobin C disease, and sickle-cell thalassemic disease, but also in persons homozygous for hemoglobin C. Hematuria is of possible significance in sickle-cell hemoglobin C disease.

Treatment of Acute Leukemia with Fluorohydrocortisone. J. M. Hill and L. Vincent. Sang **26:**269-281 (No. 3) 1955 (In French) [Paris, France].

Seventeen patients with acute leukemia of various types were treated with 9-α fluorohydrocortisone acetate. Daily massive doses theoretically equivalent to 5 or 10 gm. of hydrocortisone were used without serious side-effects. Seven complete remissions were obtained, three partial remissions, and four failures in the 14 patients who received a total of more than 250 mg. of the drug. Three other patients were admitted to hospital in the terminal stages of their disease. The action of the drug, where successful, was unusually prompt. One of the complete remissions occurred in a patient with plasmocytic leukemia. Of the 10 patients with remissions, 5 had never been treated and 4 received no other antileukemic chemotherapy during fluorohydrocortisone therapy. The drug appears capable of producing remissions in patients in whom other agents, including corticotropin administered intravenously, are no longer useful. The remissions obtained do not last any longer than those from other types of hormone therapy. Marrow examinations in this series showed an increase in the fragility and destruction of the leukemic cells and some mitotic anomalies. It is not known whether these phenomena represent a quantitative or qualitative difference of fluorohydrocortisone relative to the action of cortisone and hydrocortisone. In almost every patient there was definite stimulation of erythropoiesis with frequent passage of nucleated blood cells into the peripheral blood varying in general between 5 and 15% white elements. The platelets were not so constantly affected.

Nonsuppurative Intrathoracic Complications of Amebiasis. R. Coirault, H. Coudreau and J. Girard. Semaine hôp. Paris **31:** 1591-1602 (May 6) 1955 (In French) [Paris, France].

Difficult problems often arise in connection with the differential diagnosis of the intrathoracic manifestations of amebiasis, which may consist not only of a primary amebic abscess in the lung, without any concomitant involvement of the liver, or of an abscess localized at the base of the right lung, representing an extension into the thorax of an abscess in the liver, but also of various suppurative and nonsuppurative pleuropulmonary complications. Patients with nonsuppurative intrathoracic manifestations present three major syndromes: (1) diffuse pleuropulmonary involvement of the base of the right lung; (2) parenchymatous foci, either pneumonic or in the form of disseminated infiltrates; and (3) serofibrinous pleural effusions. Amebic hepatitis was invariably found in the authors' patients, and its detection, though often difficult, is an essential part of the diagnosis because it proves the amebic origin of the pleuropulmonary syndrome. Many of the signs and symptoms presented by the patients are subject to misinterpretation. They are often attributed to primary pulmonary disease and as a result the underlying hepatitis is overlooked. Failure to identify and treat the hepatitis, however, may be followed by abscess formation with the danger of severe suppurative complications in the thorax unless the abscess can be drained either medically or surgically. A trial treatment with emetine, which is remarkably effective in amebic conditions, may establish the diagnosis in doubtful cases. Patients with nonsuppurative intrathoracic complications of amebic origin usually recover rapidly when treated with emetine. The fever subsides, the sedimentation rate returns to normal, and the general condition improves. The clearing of the radiological findings, however, may take longer than the resolution of the hepatitis. Attention should always be given to persistence of the radiological signs in evaluating a cure, because the relief of the hepatitis may be only temporary, and its reactivation may result in further intrathoracic complications.

Suppurative Intrathoracic Manifestations of Amebiasis. R. Coirault, H. Coudreau and J. Girard. Semaine hôp. Paris **31:**1603-1617 (May 6) 1955 (In French) [Paris, France].

The suppurative intrathoracic manifestations of amebiasis fall into two groups: (1) syndromes of pulmonary suppuration with purulent vomica and (2) various forms of empyema. Recovery with complete return to health of the pulmonary parenchyma takes place in almost all patients, but more or less significant pleural sequelae are left. The suppurative manifestations of amebiasis are seldom primary, almost always appearing as complications of amebic hepatitis, which may or may not be evident. The elements that establish amebiasis as the cause of the condition are the presence of hepatitis; the macroscopic character of the pus and its abundance and sterility (except in cases of second-

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ary infection); and the spectacular improvement rapidly obtained by treatment with emetine alone. The purulent matter found in the thorax in about 80% of these patients comes from a liver abscess that has ruptured and perforated the diaphragm. Only the difficulties encountered in obtaining an accurate diagnosis of such an abscess can excuse the occurrence of this complication. Failure to diagnose and treat the hepatitis, either because the patient did not seek advice promptly or because it was masked by pleuritic or pneumonic symptoms, may result in the formation of a hepatobronchial fistula and massive vomiting of pus, differing in character according to the age of the abscess. This phase of the disorder, which rarely lasts more than three days, is followed by regression of the hepatitis and an immediate remission of the clinical signs. Treatment with emetine will complete the cure. Most amebic abscesses of the lung can be traced to pus from a ruptured liver abscess, but in some patients intrapulmonary suppuration is apparently caused by amebas that have been transported to the lungs either by the blood or the lymph. Empyema, which is the most serious intrathoracic manifestation of amebiasis, may appear abruptly, causing severe pain and shock in a patient whose general condition has been impaired by a latent hepatic abscess. Treatment for shock and prompt evacuation of the purulent matter by puncture aspiration, combined with antibiotics and antiamebic medications, will usually cure both the hepatic abscess and the empyema, although recovery may be delayed by complications such as bronchopleural fistulas and pleurisy. Empyema that is insidious in its onset may appear as a severe purulent pleurisy, or it may become encysted at the base of the right lung. Amebic empyema in all its forms usually yields to medical treatment, but it may be fatal, and even when it can be cured it has important sequelae, because the resulting retraction of the thorax and virtual immobilization of the diaphragm reduce the functional capacity of the lung.

Digestive Ailments of Older Patients. A. M. Snell. Minnesota Med. **38:**309-314 and 330 (May) 1955 [St. Paul].

Many of the gastrointestinal complaints in the aged are caused by curable or correctable lesions. Acute or reactivated peptic ulcer is relatively common in patients over 60 years of age, and both the incidence and gravity of hemorrhage appear to increase with age. Obstruction is noted in 10 to 15% of old patients with peptic ulcer. Gallstones are probably the commonest single cause of severe abdominal pain in patients over 65 years of age and neither the location nor the exact character of the pain is of much diagnostic value. As a rule the old patient with gallstones tolerates operation well and there are few contraindications. The major problem referable to the colon in old patients is constipation. The patient should be persuaded that the intestine need not be emptied every day and that no physical harm will result from an overdue stool. Diarrhea in old people is troublesome; occasionally it is associated with achlorhydria and probably also with deficient intestinal absorptive capacity. This may be relieved in part by parenteral administration of liver extract and the use of vitamin concentrates. Although complications of cirrhosis of the liver, chiefly hemorrhages from varices and episodes of hepatic necrosis, are often fatal in old persons, some of the older cirrhotic patients may survive for years in a fair state of health. In many of the patients of advanced age, the complaints, however bizarre and atypical, are likely to have an organic background. The diagnosis of the organic disease is often far from easy, chiefly because the usual clues that lead to diagnosis are absent or distorted. If the symptoms are of brief duration, full investigation is compulsory. If they are a continuation of those that have plagued the patient all his life, investigation is still essential, if only to provide the necessary reassurance and support essential to treatment. Symptomatic treatment without full investigation is risky at best, and temporizing on such a basis is the cause of much disability and many fatalities in the aged. It should not be forgotten that persons who reach the eighth decade of life are of a rather special pattern and not infrequently are made of better biological materials than their juniors. Their tolerance of operations may be amazingly good and their recovery from even major procedures rapid. Here is a field in which all physicians can participate in reducing mortality and morbidity rates and in making life more bearable for many persons who have passed their prime.

An Outline of the Newer Methods of Study of Atherosclerosis with Emphasis on the 80 to 100 Year Group. H. B. Eiber, A. A. Goldbloom, O. Deutschberger and others. Geriatrics **10:**213-220 (May) 1955 [Minneapolis].

Blood lipid determinations were made in 400 patients from 25 to 100 years of age. Roentgenograms of 650 patients were reviewed. An intensive survey was made of 75 patients, aged 80 to 100 years, with no previous histories of diabetes, or of coronary, metabolic, endocrine, or venereal disease. It was found that blood lipids contribute little to diagnosis and prognosis. The total lipids are low in the older group; cholesterol, phospholipids, and the phospholipid/cholesterol ratio are statistically inconclusive. A low lipoprotein atherogenic index may represent a current rate of atherogenesis or previously existing atherogenesis in the older age group. Determination of this index is not of any practical clinical value in the older group. There is furthermore no justification for electrophoretic or ultracentrifuge determinations in elderly patients with atherosclerosis, but the degree of dilatation of the aorta as well as the degree of calcification as seen in the roentgenogram is of extreme importance. Aortic arch calcification is increased in proportion to the degree of widening of the aorta arch. Lateral views of the abdominal aorta should be taken routinely. There is no electrocardiographic pattern typical of the aged person. Ballistocardiography is far from perfect, and the technical errors associated with it are greatly multiplied in old persons. Correlations of eyeground studies with other clinical findings are high. Total lipids, certain serum lipoproteins, the atherogenic index, the degree of aortic calcification, and the degree of aortic dilatation—all increase from youth until the "threshold" age of 60 to 75, after which there is a decline or reversal of trends. No definite conclusions are as yet available with regard to the changes taking place during the "threshold" age.

Duodenal Ulcer as an Occasional Etiologic Factor in Obstructive Jaundice. W. J. Snape. Ann. Int. Med. **42:**1001-1010 (May) 1955 [Lancaster, Pa.].

Despite the close anatomic relationship between the extrahepatic biliary system and the duodenum, jaundice is infrequently reported in patients with duodenal ulcer. In a period of three years, however, Snape observed six patients in whom duodenal ulcer was associated with jaundice. Reflection on the anatomy of the area adjacent to the duodenum suggests that the duodenal ulcer may cause occlusion of the common bile duct (1) by means of impingement of the ulcer or its inflammatory reaction on the biliary papilla—this is an uncommon mode of obstruction; (2) by compression of the common bile duct due to inflammation and edema of the pancreas resulting from a posterior penetrating ulcer since in 75% of the population the common duct travels behind the superior portion of the duodenum and is embedded in the pancreas; and (3) through involvement of the gastrohepatic ligament in deeply penetrating or perforating ulcers. The elevated alkaline phosphatases, the prompt response to vitamin K, the absence of urine urobilinogen, the prompt recession of jaundice with ulcer therapy, and liver biopsy all tend to confirm the presence of obstructive jaundice in these patients with duodenal ulcer. Moreover, surgical exploration confirmed this hypothesis in three of the patients. The author concludes that duodenal ulcer may cause obstructive jaundice in some patients.

Treatment of Pain in Cancer Patients. F. Fabris. Presse méd. **63:**727 (May 14) 1955 (In French) [Paris, France].

Thirty-two patients with neoplasms causing pain were treated with promethazine and chlorpromazine in addition to the analgesics they habitually received. The addition of the two drugs caused a decrease in the amount of analgesics required. Toxic reactions to promethazine and chlorpromazine were minimal. The former drug has a powerful antihistaminic and hypnagogic

effect, while the latter produces psychosomatic dissociation with effects comparable to those of lobectomy. The improvement in general well-being was striking in these patients. Tumors that are ulcerated, infected, or threatened (because of irradiation) with localized inflammatory reactions benefit the most from this treatment.

Application of Homeostatic Principles to the Practice of Parenteral Fluid Therapy. N. B. Talbot, G. A. Kerrigan, J. D. Crawford and others. New England J. Med. **252:**856-862 (May 19) and 898-906 (May 26) 1955 [Boston].

In patients undergoing parenteral therapy with fluids, as in those taking food and fluids orally, the body's homeostatic systems may be expected to function satisfactorily only if necessary constituents are provided in reasonably generous and yet physiologically tolerable amounts. This report is concerned with the physiological characteristics and clinical use of dextrose in water; 0.85% sodium chloride in 5% dextrose solution; saline lactate in 5% dextrose solution (a liter of this solution is prepared by mixing 30 ml. of molar sodium lactate, 750 ml of 5% sodium chloride in dextrose, and 220 ml. of 5% dextrose in water); and a potassium-containing multiple electrolyte solution in 5% dextrose. Successful use of the suggested guides to therapy depends on careful appraisal of the status of the particular therapeutic needs of each patient. To permit the application of therapeutic considerations to patients varying in size from the premature infant to the adult, most of the values are expressed in terms of square meter of body surface per unit of time. The approximate surface area of patients of various weights may be estimated with the aid of a table, which lists 0.15 square meters as the surface area equivalent of an infant weighing 4.4 lb. (2,000 gm.) and 2.05 square meters as the surface area equivalent of a person weighing 220 lb. (100 kg.). It is concluded that the application of homeostatic principles should make it possible both to improve and to simplify the practice of parenteal fluid therapy.

Interrelationship of Acute Alkalosis and Potassium Metabolism: A Clinical Study. C. R. Kleeman, M. E. Rubini, E. Lamdin and others. Metabolism **4:**238-249 (May) 1955 [New York].

A 35-year-old woman who ingested 200 cc. of an antifreeze compound containing 80% methyl alcohol, with suicidal intent, was given intravenously 1,600 mEq. (about 27 mEq. per kilogram of body weight) of hypertonic sodium bicarbonate (2,700 cc. of a 5% solution) within three hours. Her severe acidosis on admission to the hospital was rapidly converted in a marked metabolic alkalosis associated with the risk of overtreatment but justified because of the grave prognosis of untreated methanol intoxication. Her acute metabolic alkalosis was associated with potassium depletion that potentiated the original metabolic alkalosis. At the height of the potassium depletion her urine became acid despite severe extracellular alkalosis. She vomited four times in the 10th to 20th hours of hospitalization but felt well thereafter. Fluid diet supplemented with parenterally given solutions containing 5% dextrose and potassium was given on the second hospital day, after which a full hospital diet was tolerated. Coincident with potassium repletion there was a further increase in the patient's urinary excretion of ammonia and titratable acid. This sequence of events is consistent with the view that alkalosis secondary to potassium depletion is associated with an intracellular acidosis and that the "paradoxical" aciduria potentiates, but is not the cause of, hypokalemic alkalosis. The continued excretion of ammonia in an alkaline urine associated with extracellular alkalosis emphasizes that factors other than the pH of urine and/or extracellular fluids are important stimuli for ammonia production. The patient was discharged asymptomatic from the hospital on the fifth day.

Safer Pneumoperitoneum Refills. J. B. Devine and E. Dunner. Dis. Chest **27:**553-557 (May) 1955 [Chicago].

The authors show that the physician inducing a pneumoperitoneum should pay attention to the phase of respiration during which the needle is introduced into the abdominal cavity. The height of the abdominal air space in a patient with artificially induced pneumoperitoneum is increased on deep inspiration as compared with expiration. It is therefore concluded that for those patients receiving pneumoperitoneum refills in whom an appreciable air space is not present, the insertion of the needle at the end of a deep inspiration is safer and reduces the danger of injuring the abdominal viscera.

SURGERY

A Maneuver for Extracting Clots from the Atrium at the Time of Mitral Commissurotomy: With Reports of Four Consecutive Cases. W. L. Jamison, K. V. S. Rao and C. P. Bailey. J. Thoracic Surg. **29:**541-551 (May) 1955 [St. Louis].

The usual technique of performing commissurotomy is to enter the left atrium with the right index finger through an incised area in the left auricular appendage that has been previously enclosed by a purse-string suture. Commissurotomy may be performed either with the guillotine knife or merely by digital pressure. One of the most dreaded complications is that of finding a ball thrombus in the auricle attached by a thin pedicle and waving freely in the blood stream. These clots may be 3 to 4 cm. in diameter. During any manipulation of the left auricular appendage, the left common carotid artery and the right innominate artery are clamped. While this technique has reduced the hazard from clots as far as emboli to the brain at the time of operation are concerned, the postoperative threat is still present if the clot is not removed. The authors describe a maneuver that one of them (W. L. J.) used to remove clots successfully in four consecutive cases during the past six months. This maneuver comprises three steps: (1) compressing the clot between the ungloved index finger and auricle; (2) extracting the clot by finger traction and grasping with a Kelly clamp; and (3) getting rid of any loose particles by allowing the unclamped auricle to bleed freely during the time between pronation and supination of the hand. In the first of the four patients the auricular appendage was so small that the surgeon was able to insert only the fifth finger. Jamison found this a safe and efficient method of dealing with a small, thrombosed appendage. If the fifth finger does not have sufficient strength to open the valve, a guillotine knife can then be used. In the second patient, who had Raynaud's disease in addition to rheumatic fever, an attempt was made to wash out any clots in the atrium by merely opening the Satinsky clamp. This proved ineffectual in that a large clot was subsequently palpated in the left atrium. This shows the need for an additional technique to deal with these clots rather than merely bleeding the appendage. In case 3, flushing the appendage by opening the Satinsky clamp was sufficiently effective to enable the operator to get his finger to the valve. All loose clots in the appendage were removed by this maneuver. The large atrial clot was palpated after a commissurotomy and was in the posterior superior aspect of the atrium. In case 4, the clot was small, and its extraction was much easier in that the diameter of the index finger was slightly wider than the diameter of the clot, but a clot of this size in the cerebral or popliteal artery could easily cause death of the tissue involved.

Resection and Anastomosis of the Bronchus Carried out in a Case of Benign Tumor. A. Bikfalvi and S. Dubecz. J. Thoracic Surg. **29:**488-496 (May) 1955 [St. Louis].

Bronchoscopy revealed a tumor in the right main bronchus of a 42-year-old man. Although a biopsy suggested "oat cell carcinoma," the patient's favorable general condition and his long history interspersed with suppurative symptoms and hemoptyses suggested the possibility of a bronchial adenoma, and this was corroborated by a new bronchoscopic examination and by histological studies of a biopsy specimen. In order to save the middle and lower lobes, the authors decided on a bronchoplastic operation. After inducing an artificial pneumothorax, a thoracotomy was performed. In the course of the operation, the upper lobe bronchus was amputated, and through this bronchotomic aperture the part of the tumor that occluded the orifice of the

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upper lobe bronchus could be seen. Then the bronchus was cut transversely, nearly at a level with the carina. The bottom level of the transverse section was 1 cm. above the point of origin of the middle lobe bronchus. To avoid disproportion of the two lumina, the intermediate bronchus was amputated in an oblique direction. Then an end-to-end anastomosis was performed with thin and everted mattress sutures of silk, stitching up the paries membranacea of the bronchus to achieve uniformity of the lumen of the bronchus. The suture line was closed hermetically, and no narrowing of the caliber was observed. The removed section of the bronchus measured about 30 mm. The suture line was covered with mediastinal pleura dissected from the region of the vena azygos. The thorax was then closed and drained by two de Pezzer catheters. By resecting the right main bronchus and the intermediate bronchus and bridging over the resulting break by an end-to-end anastomosis it was possible to preserve the function of the middle and lower lobes, and avoid a mutilating pneumonectomy. Six months later the patient was free from symptoms and had resumed his former occupation. The case proves that a large segment of one of the main bronchi can be removed and an anastomosis can then be made without inserting a prosthesis or a graft. Although other reports indicate that at most 2 cm. can be resected, in this case the resected portion of the bronchus measured 3 cm. An artificial suture line, avoidance of overtautness, an anastomosis free from stenosis, and quick expansion of the lung are important factors in the success of this operation.

The Masked Bronchopleural Fistula. B. J. Franz and J. D. Murphy. J. Thoracic Surg. **29:**512-517 (May) 1955 [St. Louis].

The symptoms and signs of postresection bronchopleural fistulas occasionally develop in a manner not suspected until a catastrophe supervenes. Failure to detect such a fistula is likely when surgeons must leave the postoperative care to staff members who are not aware of the dangers that lurk in the "alveolar leak," "space defect," "reluctant reexpansion," or any of the other euphemistic terms that are used to describe this complication. The authors apply the term "masked fistula" to lesions that become evident after a period in which the patient seems to progress satisfactorily. On the basis of statistics from Veterans Administration Hospitals, the authors demonstrate the gradually increasing incidence of segmental resections, as compared to pneumectomies and lobectomies, and they believe that with the increase in segmental resections, the possibility of small alveolar air leaks is augmented. A masked fistula developed following 24 of 625 pulmonary resections, which were performed between 1945 and 1953. The subjective signs most helpful in suspecting a masked fistula are: pain or tightness in the chest, a sensation of blowing air in the pleural cavity, and an increase of red or brown sputum when the patient lies on the side not operated on. Objective signs include: return of fever, roentgenologic evidence of an unabsorbed or increased amount of intrapleural air or the appearance of an air pocket in a new location, unexplained lowering of the intrapleural fluid level, increase in bloody sputum or fluid expectoration after instillation of fibrinolytic agents, expectoration of instilled dyes, smell or taste following instillation of an odor-producing material such as ether into the pleural cavity, bronchoscopic visualization of a fistula, bronchographic demonstration of an abnormal communication between the bronchial tree after injection into a chest wall sinus, subcutaneous emphysema, demonstration of an inexhaustible "air pocket" on thoracentesis, sudden appearance of a pneumothorax after reexpansion of the lung, and failure of the remaining lung to reexpand. A residual pleural space following any form of pulmonary resection could be an occult bronchopleural fistula, and every effort should be made to prove its existence in order to institute treatment and forestall serious complications. Since recognition of these fistulas is often difficult, available tests should be repeated as often as necessary. The initial failure of a test does not mean it will subsequently fail. It is suggested that any patent pleurocutaneous sinus be repeatedly investigated and considered as a possible omen of bronchopleurocutaneous communication.

Traumatic Chylothorax and Thoracic Duct Ligation: Case Report and Review of Literature. J. Goorwitch. J. Thoracic Surg. **29:**467-479 (May) 1955 [St. Louis].

A 44-year-old woman had swelling of the face, neck, and upper chest and x-ray evidence of a left hydropneumothorax. Three days earlier she sustained an accidental stab wound to the neck, which drained milky fluid and relatively little blood and which was repaired on the day of the accident. On the basis of aspiration of this milky fluid from the left pleural cavity a diagnosis of chylopneumothorax was made, and this diagnosis was confirmed by the demonstration of fat globules taking up Sudan 3 stain and by ether extraction of fat from the pleural fluid. Although therapy was directed toward support of nutrition and promotion of spontaneous sealing of the chylous fistula, a tendency toward early encapsulation and insufficient drainage became evident. As the patient's general condition began to deteriorate, it was decided that despite the fact that the chylous fistula was cervical rather than intrathoracic and even though the loss of chyle appeared to be diminishing spontaneously, the presence of clotted chylothorax called for operative intervention. Seventeen days after the injury, a left thoracotomy was performed. The left lung was collapsed against the mediastinum. About 3 liters of pink chylous fluid and several handfuls of semiclotted gelatinous material were removed, and decortication of the lung was performed. The "peel," measuring up to 2 mm. in thickness, was thickest over the lower lobe. Reexpansion of the lung was complete. During this portion of the operation chyle could be seen accumulating slowly in the superior portion of the pleural cavity. Following limited mobilization of the esophagus mesial to the aorta, the left vagus nerve and a single thoracic duct were identified. The latter was isolated and ligated with 000 black silk. Ten months after the operation the woman had no symptoms and was doing her regular work. Increasing interest in traumatic chylothorax is due both to the safety and success of intrathoracic ligation of the thoracic duct as well as to the increasing frequency of this lesion as a complication of operations in and about the mediastinum. A total of 17 patients with traumatic chylothorax have been subjected to ligation of the thoracic duct. This was always followed by recovery, and there was no unusual morbidity. By contrast, a mortality of 19% was found among the patients in whom chylothorax was treated by methods other than by ligation of the thoracic duct. Ligation of the thoracic duct is the treatment of choice when after a brief period of management by aspiration or continuous closed drainage the chylous fistula shows no tendency to seal off spontaneously.

Eosinophilic Granuloma of Ribs: Review of Literature and Report of Two Cases with Four and Six and One-Half Year Follow-Up, Respectively. J. F. O'Neill, S. J. Skromak and P. R. Casey. J. Thoracic Surg. **29:**528-540 (May) 1955 [St. Louis].

Eosinophilic granuloma of bone, although possibly a form of Letterer-Siwe's and Hand-Schüller-Christian's syndromes, and possibly related to syndromes where bone and skin, or bones and lungs are involved, can occur in one or more sites limited to the skeleton and can run a chronic benign course with complete healing. To date about 189 patients with eosinophilic granulomas of bone have been reported in the literature including the two presented here. Both of the reported patients were entirely well, four and six and one-half years, respectively, after resection of the involved rib segments. The finding of a single eosinophilic granuloma in one bone necessitates a complete skeletal survey and a careful search for involvement of the skin, lymph nodes, bone marrow, lungs, liver, and spleen or any evidence of diabetes insipidus, exophthalmos, or mental retardation. In all patients whose lesions are limited to the skeleton, healing will probably occur, the outlook improving with the age of the patient. In infants and children the prognosis must always be guarded in view of the possible development, months to years later, of Letterer-Siwe's or Hand-Schüller-Christian's syndromes. In adults, the prognosis, although better than in children, should be guarded because of nonhealing, recurrences, new lesions, or

involvement of the lungs or skin. Eosinophilic granuloma of bone is diagnosed by biopsy only. Surgical treatment is probably best limited to biopsy or treatment of sequelae. X-ray treatment of lesions may relieve pain and aid in repair. Its use seems indicated until a better method becomes available.

Relapse After Pulmonary Resection During Prolonged Streptomycin-Para-Aminosalicylic Acid Treatment of Pulmonary Tuberculosis: An Analysis of 9 Relapses in 82 Cases. L. H. Capel and R. S. Mitchell. Am. J. Med. **18:**557-560 (April) 1955 [New York].

Of 82 patients with pulmonary tuberculosis who were subjected to pulmonary resection in the course of prolonged treatment, but for less than 12 months, with 1 gm. of streptomycin intramuscularly twice weekly and 12 to 16 gm. of *p*-aminosalicylic acid (PAS) by mouth daily, 11 relapsed at some time after the resection. Two of the 11 patients were seriously ill at the time of the resection and are not considered in the authors' report. Of the other nine, five were receiving combined treatment with streptomycin and PAS for the first time and four were receiving retreatment with these two drugs. Since in each of these nine patients the disease became active again at or near the site of the operation, it is suggested that the surgeon's knife may have been in part responsible for the relapse. This possibility is supported by the occurrence of relapse immediately after the resection and in the course of continued chemotherapy in two patients. Organisms from the tissue of one of these were found to be susceptible to streptomycin and PAS. In a third patient, who had bilateral disease at the outset, worse on the left, all the visible and palpable lesions on the left side were resected. Endobronchial disease was observed microscopically at the margin of the resected specimen. Relapse occurred at the site of operation and not on the opposite side. The total of only three months' chemotherapy doubtless contributed to failure in this case. Potentially dangerous visible and palpable lesions may be removed at the expense of damaging adjacent lung tissue containing invisible and impalpable lesions. This damage may reduce the ability of the lung to hold this remaining disease in check. If living tubercle bacilli are observed in resected tissue, they may also be left behind. Thus inadequate duration of chemotherapy for less than 12 months and the creation of a favorable environment for the growth of tubercle bacilli by operative tissue damage were believed to be related causally to these relapses. The selection of patients for pulmonary resection during prolonged combined treatment with streptomycin and PAS should be based on clinically demonstrated necessity rather than on the immediate safety of the operation. It is necessary to remove the persistently open cavity, which presents great mechanical impediment to healing and from which drug-resistant organisms will probably emerge. When indicated and feasible, resection should be performed early in the course of retreatment with streptomycin and PAS. Patients receiving retreatment with open cavities are in greater danger from resection than are patients with cavities who are treated originally, probably because of the more rapid emergence of drug resistance during retreatment with streptomycin and PAS. The significance of this observation increases as operation is delayed.

Extended Sympathectomy in Arterial Hypertension: I. Immediate Results on the Basis of 122 Interventions. R.-H. Martin and M. Bonamy. Arch. mal. coeur **48:**240-244 (March) 1955 (In French) [Paris, France].

The authors use an expanded Poppen operation that permits the removal both of sympathetic chains containing 10, 11, or even 12 ganglions and of the splanchnic nerves from beginning to end. The kidney is exposed to permit removal of a biopsy specimen, which should be as deep as possible. Histological examination of such specimens has invariably revealed lesions in the glomeruli, tubules, or interstitial tissue. Unilateral adrenalectomy or adrenal medullectomy is now being combined with the ablation of the sympathetic chains. The surgical treatment of hypertension by this method requires from four to six weeks of hospitalization and several months of convalescence; only patients capable of resistance can withstand the serious shock of the procedure. Analysis of the results obtained in 122 patients (225 operations) shows that the 12 immediate postoperative deaths all occurred in the first half of the series when patients were not rigidly selected and several operations were performed in an attempt to save the lives of the patients regardless of their age or the extent of their renal lesions. No deaths occurred among patients who were under 35 years of age. Careful selection, an upper age limit of 40 years, and constant supervision by thoroughly trained personnel during and after the intervention are essential if the operation is to be performed without notable risk to the patient. Observance of these requirements will smooth the postoperative period, which otherwise is apt to be difficult. Early complications usually appear as a pronounced aggravation of one of the clinical symptoms seen during the first days after the operation, e. g., intercostal pain, dyspnea, viscid and sometimes painful expectoration, a febrile syndrome with tachycardia, and dyspnea relieved by transfusions but not by antibiotics. More serious complications, such as pleural effusions, hemiplegia, cerebral edema, and cardiovascular disturbances are rare and usually transient; only three deaths in this series were due to complications of this kind. Severe orthostatic hypotension, which may be due to overextension of the sympathectomy, especially in the lumbar zone, did not appear in these patients. These results show that the decision to operate on young adults with severe hypertension resistant to medical treatment should be based, not on technical considerations, but on the developmental tendencies of the disease, the choice of patients, and the late results of the procedure.

Extended Sympathectomy in Arterial Hypertension: II. Late Results. F. Joly, A. Mathivat, J.-R. Sicot and others. Arch. mal. coeur **48:**245-276 (March) 1955 (In French) [Paris, France].

The effect of extended sympathectomy on patients with arterial hypertension can only be interpreted when the postoperative pressure readings are considered in connection with the changes in the general and functional signs and the visceral lesions. Patients who survive the operation may be divided into (1) those in whom all signs of hypertensive disease regress; (2) those in whom the arterial pressure remains irreducible, but all other hypertensive disturbances disappear; (3) those in whom the operation is without effect; and (4) those in whom improvement is only temporary. Follow-up of 80 patients ranging in age from 18 to 53 showed that 5 died after the first or second stage of the operation; 18 died from one month to 5 years after the operation; and 57 were still alive from two to six years after it. Malignant hypertension, unaffected by the operation, was responsible for 15 of the late deaths. The other three followed complete or partial remissions lasting five years or more. The 19 patients in group 1 and the 17 in group 2 were able to resume normal activity within a few months, or one year at the most, after the operation. All but two of the 17 in group 3 were over 40 years of age and all had severe impairment resulting from their disease. The radiological and electrocardiographic changes, which were particularly frequent in this group, were not influenced by the operation, but retinal changes (hemorrhage with or without papilloretinal edema) disappeared completely in 8 of the 10 patients in whom they were present. Group 4, in which the hypertensive syndrome reappears after a complete remission, is important from the prognostic point of view, because, before the recurrence takes place, everything seems to point to the success of the operation. Some of the patients in group 1, therefore, may later have to be added to the five now listed in group 4. The postoperative findings in this series show that (1) the drop in pressure is often transient in character; (2) the clinical and manometric findings are not always in agreement; and (3) the period of postoperative stabilization of the disease varies with each patient. All attempts to establish precise indications for sympathectomy in patients with hypertension have so far failed, and the results of the operation are so often transitory that it should be reserved for patients in whom other methods of treatment have proved unsuccessful and in whom it is not contraindicated by age or other adverse conditions.

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Stasis Ulcers: An Evaluation of the Effectiveness of Three Methods of Therapy and the Implication of Obliterative Cutaneous Lymphangitis as a Credible Etiologic Factor. C. A. Moyer and H. R. Butcher Jr. Ann. Surg. **141:**577-588 (May) 1955 [Philadelphia].

Investigations were undertaken to evaluate the following methods of treating chronic ulcers of the leg: (1) the injection or ligation of varices and the wearing of Unna's boots, elastic bandages, or elastic stockings: (2) the injection or ligation of varices, the wearing of elastic supports, and the grafting of the ulcer without excision or after its excision, with only a narrow band of surrounding skin; and (3) the ligation, excision, or stripping of varices; the immediate split grafting of the cutaneous defect after the excision of the ulcer and all thickened skin and fascia about it; and the wearing of elastic supports thereafter. The third method was best, and the second method was better than the first. The likelihood of failure with the third method is the greater the larger the ulcer, the greater the number of ulcers, the more evident the postoperative edema, and the poorer the take of graft or the slower the epithelization in small localized primary graft failures. Age, sex, nutritional status, history of antecedent phlebitis, duration and position of the ulcer, the extent of varices, the presence of preoperative edema, and the type of prior therapy had no apparent relationship to the success or failure of the third method of treatment. The use of the third method whether successful or not did not place life, limb, or health in significantly greater jeopardy than they were in before the treatment was instituted. The authors urge that (1) absorbable ligatures be used for hemostasis; (2) the excision include the base of the ulcer together with all surrounding inelastic skin and thickened fascia; (3) the defect be covered immediately with a split-thickness cutaneous autograft; (4) the feet and legs remain on the bed for from 14 to 21 days, since dependency of the leg before the 14th day is attended by lifting of the graft from its base by confluent petechial hemorrhages; and (5) elastic supports be worn indefinitely. Whereas the dermal lymphatics were found obliterated in the skin adjacent to stasis ulcers, they were present and initially dilated in the successful skin grafts. The superficial lymphatics of the grafts soon established connections with the dermal lymphatics of the skin about them. In areas adjacent to ulcers arising after primary graft take, no lymphatics were patent, but to date, no recurrent ulcer has appeared in any area of a graft shown to possess lymphatics.

The Management of Bleeding Esophageal Varices Associated with Cirrhosis of the Liver. J. E. Hamilton. Ann. Surg. **141:** 637-647 (May) 1955 [Philadelphia].

The varices associated with cirrhosis of the liver are secondary to the increased pressure caused by intrahepatic portal obstruction, but since it is not clear just how this portal obstruction is produced Hamilton summarizes the chief working hypotheses and the different therapeutic plans arising therefrom, particularly the views on hepatic artery ligation and portal systemic shunts. If esophageal bleeding is at an alarming rate or does not respond promptly to bed rest and transfusion, double balloon tamponade has become the first line of defense against exsanguination. In spite of his earlier enthusiasm and the encouraging reports on its use by others it has proved disappointing to the author, in that bleeding was not controlled in 11 of 20 patients, and 15 of the 20 patients died during the hospitalization in which double balloon tamponade was tried. He suggests that the results might be improved by more heroic blood replacement and earlier resort to ligation of varices. Of the various procedures that have been tried in the treatment of varices including packing the superior and posterior mediastina with gauze to stimulate collateral circulation, stripping the outer surface of the lower esophagus of its blood supply, plus vagotomy, resection of part or all of the stomach to prevent regurgitation of acid contents into the esophagus and erosion of varices, hepatic arterial ligation, and portal-systemic shunts, the author considers the last the most feasible, but states that arterial ligation has received much attention of late. Reviewing the experience of 14 authors with ligation of the hepatic artery, splenic artery, and sometimes also the left gastric artery, in treating hemorrhage and ascites associated with cirrhosis, he found that among 87 patients 23 died in the hospital and at least 10 more deaths occurred within a year after operation. Bleeding recurred in 60% of the patients. The author therefore questions the safety and efficacy of this procedure. Twenty-nine portacaval shunts and four splenorenal shunts performed on dogs in the laboratory were the background for eight such operations that the author performed on human subjects. If the spleen is large he prefers splenectomy and splenorenal shunt because: (1) the large spleen assures an adequate-sized vein and anastomosis; (2) splenectomy will obviate hypersplenism; and (3) the procedure is slightly the safer of the two. On the other hand, if the spleen is relatively small, a portacaval anastomosis is advisable as it assures a stoma at least 1.5 cm. in diameter. If the portal vein and vena cava are widely separated one may decide between an end-to-side shunt with ligation of the proximal stump of the portal vein or a femoral vein graft between the two veins. One of four patients who were good risks and two of four who were poor risks died. Except for one minor and unverified episode, none of the five who survived bled further. Their general health and liver function, following a temporary decline after operation, returned to a level not significantly better or worse than before the operation.

Indications and Late Results of Ligation of Inferior Vena Cava. J. A. Kirtley Jr., D. H. Riddell and E. C. Hamilton. Ann. Surg. **141:**653-663 (May) 1955 [Philadelphia].

Ligation of the inferior vena cava was performed on seven different indications in 34 patients. Multiple pulmonary emboli was the indication for ligation in 19; other indications were: massive infarction with obscure origin of embolus, ascending thrombosis of the lower extremity above the inguinal ligament with embolus; accidental trauma to the inferior vena cava, septic pelvic thrombophlebitis, embolism in which anticoagulants were contraindicated, and in some patients prophylactic ligation performed during abdominal exploration. The authors regard these indications as valid. Their belief that venous ligation at a level lower than the inferior vena cava is not justified was substantiated. Extraperitoneal operation is regarded as the best technique for ligation of the inferior vena cava. In the postoperative period circular elastic bandages are applied from the base of the toes to the groin bilaterally. The foot of the bed is elevated on 6-in. blocks, and the patient is kept at bed rest for two weeks, being allowed up to void or to sit up for meals only. The authors no longer believe that anticoagulants are essential during the postligation period. Bicycle exercises of the legs are begun during the second week, while the patient is still in bed. Four patients died during the operation. Nine patients have died in all, and one could not be followed. Twenty-two of the remaining 24 patients were capable of normal activity when last seen. Fourteen of the patients have been followed from 25 to 85 months, and the late disabling sequelae (severe edema, ulceration, dermatitis, and pain) were found in only two patients. Those lower extremities with preligation evidence of thrombophlebitis have more serious sequelae than those extremities that were free of disease before ligation. The authors believe that the low incidence of late deleterious effects of vena caval ligation should encourage its use when a true indication for ligation exists.

Use of Reenforcing Metallic Mesh Gauze in Repair of Large Postoperative Ventral Hernias. T. J. Floyd Jr. J. M. A. Georgia **44:**225-228 (May) 1955 [Atlanta, Ga.].

The author performed 14 postoperative ventral hernioplasties using tantalum mesh wire as reinforcing suture material. The ages of the patients ranged from 31 to 73 years (average 52). There were 4 men and 10 women. Four had upper abdominal hernias (each following a cholecystectomy, two with a split rectus incision and two with a transverse incision); of the other 10, one had a recurrent inguinal hernia, and nine had subumbilical hernias. Of these nine, three hernias occurred after appendectomies with split rectus incisions, and six after pelvic operations with midline incisions. Of these 14 patients one had a recurrence. There were no deaths in this series. The author

believes that the use of this reinforcing material allows of much better results than could be obtained with older methods in the old, weak, obese, poor risk type of patient who is prone to postoperative ventral hernia.

Perforation of the Rectosigmoid Colon Due to Straining. M. P. Birbis. Bordeaux chir., pp. 17-25 (Jan.) 1955 (In French) [Bordeaux, France].

A report is given of four men in whom perforation of the rectosigmoid colon occurred on straining. These patients, whose ages ranged from 38 to 69 years, had suffered from constipation prior to the rupture but had no other complaints referable to the digestive tract. The perforations had a punched-out appearance and were located on the free edge of the sigmoid or rectosigmoid region. In three patients a large, hard stercoroma was found in the pararectal pouch. It would seem that a hernia forming in a weak spot in these chronically constipated patients must be the basic cause of the rupture. Hemorrhage from the rectum, severe abdominal pain, and other signs of peritonitis such as fever follow the rupture. All the patients recovered after surgical closure of the perforation; one died in cachexia resulting from a neoplasm of the larynx, and the others were cured.

Thoughts on Early Diagnosis and Recent Trends in Treatment of Lumbar Pott's Disease in the Adult: With Reference to 82 Cases. S. De Sèze, S. Rampon and C. Guérin. Semaine hôp. Paris **31:**1712-1729 (May 20) 1955 (In French) [Paris, France].

The fact that patients with tuberculosis of the vertebrae (Pott's disease) can now be safely operated on under the protection of chemotherapy increases the importance of early diagnosis, because complete removal of the tuberculous focus is possible if the operation is performed while the lesions are still localized. Study of 103 patients with Pott's disease showed that in 82 the condition was localized in the lumbar spine and that the lumbosacral joint was affected oftener than any other part of the spinal column. Most (60%) of these 82 patients were young adults, 31.5% were in the 40 to 60 year age group, and 8.5% were over 60. The diagnostic signs—abscess in the iliac fossa, incipient paraplegia, and psoitis—mentioned in the standard descriptions of Pott's disease were rarely seen; pain, on the other hand, which is usually said not to be present, was in all patients the first symptom noticed. It was found in two principal forms—ordinary backache and referred crural or sciatic pain. The clinical investigation of patients in whom Pott's disease is suspected should consist of (1) an examination of the spine, (2) a neurological examination, (3) a search for abscesses, (4) study of the general signs and of the biological signs of inflammation, and (5) study of the history and a search for other tuberculous foci. The results of this investigation, however, though helpful, are seldom conclusive, because neither the characteristic stiffness of the spine nor any of the other signs suggestive of Pott's disease can be constantly detected. Radiological study, on the contrary, provides a secure basis for the diagnosis by demonstrating the spondylodiskitis that constitutes its fundamental lesion. Some evidence of a change in the intervertebral space is always visible on the standard x-ray films in patients with Pott's disease, but when the reading of the films is complicated by the existence of a congenital malformation or some other condition, tomography may be used to clarify the diagnosis. Puncture biopsy of the vertebral body and direct surgical exploration of the lesion sometimes serve as useful supplementary measures in doubtful cases. Treatment may be either medical or medical and surgical. Chemotherapy usually produces a rapid improvement in the patient's general condition, but since the period of immobilization can be substantially shortened and the quality of the cure improved by removal of the tuberculous focus, the authors advocate the combined method, in which the medical treatment is intended to prepare the patient for the operation and to consolidate his recovery afterwards.

The Problem of the Broken Judet Prosthesis. K. H. Pridie. J. Bone & Joint Surg. **37B:**224-227 (May) 1955 [London, England].

In using the Smith-Petersen cup operation in arthroplasty of the hip, the author had learned that the blood supply of the stump of the femoral neck was the all-important factor in determining the end-result. When Judet (1950) introduced the acrylic prosthesis it seemed to the author far sounder to get rid of that part of the bone in which the circulation was endangered either by a vascular calamity or by sclerotic changes in the bone itself, and he decided to try the Judet arthroplasty. The immediate results were better. The patients became ambulatory earlier, and the range of movement was superior to that after the cup operation. This improvement was only transient, continuing through the first and sometimes the second year. At about this stage the improvement after the Judet operation appeared to halt, and complications began to appear. A falling off of performance in a previously satisfactory hip and the gradual reappearance of pain and muscle spasm became evident. The radiograph at this period suggested that the prosthesis was loose. Then, on watching these patients for several months, occasionally a typical fracture of the prosthesis that resembled an intracapsular fracture of the femur would be observed. The author has encountered five broken prostheses in a series of about 100 patients. He believes that the acrylic head prosthesis operation should be abandoned for any patient who intends to lead an active life. The orginators of the operation have discovered that it was not universally satisfactory, and they have changed their prosthesis to an oblique-angled femoral head, still made of methyl methacrylate. Eighty per cent of the author's patients are satisfied, and he believes that the operation is a good one, but the material of the prosthesis has been found wanting. It must be expected that fracture of the prosthesis will occur in about 10%, and as time goes on the number might be greater. With regard to the treatment of these patients the author says that in the early stages, when radiographs show that the stem is eccentric, three months in plaster might allow the prosthesis to gain sufficient fixation with fibrous tissue to afford relief, but if this does not help, the operation should be revised and a more durable type of prosthesis used. A Küntscher or Watson-Jones nail is not strong enough and will break in time. An alternative solution in patients with fractured prosthesis lies in the Girdlestone (1945) operation, which is final and introduces no new foreign substance that may break and no substance that will wear.

Present Status of Surgical Treatment of Varicose Veins with Special Emphasis on Vein Stripping. C. A. Griffith and H. N. Harkins. West. J. Surg. **63:**245-252 (May) 1955 [Seattle, Wash.].

Surgical vein stripping for the treatment of varicosities was introduced before World War I, more or less abandoned between the two wars, and revived after 1937. Essential to the success of this therapy is coincident high ligation and thorough division of the branches of the greater saphenous vein at the region of the fossa ovalis. Most patients with varicose veins severe enough to warrant operation will benefit most from a surgical procedure that may include: (1) high ligation of the saphenous vein at the fossa ovalis, (2) ligation and division of all branches at the saphenofemoral junction, (3) careful inclusion of both branches of a bifid saphenous, (4) stripping of the greater saphenous vein from groin to ankle, (5) excision of large varicose branches and plexuses, and (6) stripping of the lesser saphenous vein. From these six fundamental procedures, a choice can be made for individual treatment of the patient with varicose veins.

Pseudo-Metastases (Benign Tumors in Patients Previously Operated on for a Malignant Neoplasm). A. C. De Vet and H. A. D. Walder. Arch. chir. neerl. **7:**78-84 (No. 1) 1955 (In English) [Arnhem, Netherlands].

When a neoplasm develops in a patient previously operated on for malignant tumor, it is generally assumed that the new growth is a metastasis. Benign tumors may develop in patients who have been operated on for cancer. The authors observed three such patients within two months, which proves that it is by no means a rare occurrence. The patients in question had

benign tumors of the spinal column. This points up the necessity of differentiating between metastases and benign processes of the spinal column. The metastatic nature of a neoplasm should be doubted if the patient's general condition is good. In patients with metastasis in the spinal cord paresis generally precedes sensory disturbances. Metastases in the spinal column or cord nearly always give rise to violent pain. Such pain was present in two of the reported patients and therefore could not serve as a differentiating symptom. Metastases to the spinal cord can generally be ruled out in the absence of radiological changes. Metastases are generally associated with an increased sedimentation rate, and the blood calcium and phosphatase values are also often increased. These values were normal in the reported patients. The fact that carcinomas of bladder and rectum hardly ever give rise to metastases in the spinal column should also be taken into account.

Hyperparathyroidism. W. F. Suermondt. Arch. chir. neerl. **7**:1-16 (No. 1) 1955 (In English) [Arnhem, Netherlands].

The most important finding in hyperparathyroidism is hypercalcemia, accompanied by hypophosphatemia, hypercalciuria, and hyperphosphaturia. The alkaline phosphatase content of the blood rises as the severity of the osseous changes increases. A low calcium content of the cerebrospinal fluid supports the diagnosis. The protein content of the blood and the renal function should likewise be investigated, because they are important for a correct diagnosis. In the presence of severe renal lesions, the calcium content of the blood may be reduced to normal values as the result of the retention of phosphates. During the operation all four parathyroids should be exposed, because adenomas may be bilateral; this was the case in 2 of 13 patients in the author's series. Impairment of the renal function and increase in blood pressure make the prognosis more unfavorable. The diagnosis should be made early, and treatment should be instituted before irreversible renal lesions have developed, because the latter will become more severe, even after the hyperparathyroidism has been cured by extirpation of the adenoma.

GYNECOLOGY & OBSTETRICS

Treatment of Trichomonas, Monilia and Mixed Infections of the Vagina. A. Saucier and R. Simard. Canad. M. A. J. **72**:584-585 (April 15) 1955 [Toronto, Canada].

Propi-Vaginal is a vaginal suppository containing sodium propionate, propionic acid, and diiodohydroxyquinoline with added lactose, dextrose, boric acid, and lactic acid. This agent was used in the treatment of 41 patients with vaginitis due to Trichomonas or Monilia organisms or both. A vaginal smear was obtained from each patient, after which a 15-day treatment with three suppositories a day for 3 days and two a day for 12 days was instituted. Then another smear was taken, but treatment was continued with one suppository a day for 15 days regardless of smear findings. After this 30-day treatment period another control smear was taken, and finally, 15 days later, a last control examination was made. If the second control smear was still positive, treatment was continued with one suppository daily for 15 days, at the end of which period another smear was taken. This procedure was repeated until a negative result was obtained. Not one case of pain or erythema from the drug occurred in this series. Complete cure was obtained in about 80% of cases. The five patients whose smears remained positive or reverted to that state were the most careless in their personal hygiene.

Hemophilus Vaginalis Vaginitis: A Newly Defined Specific Infection Previously Classified "Nonspecific" Vaginitis. H. L. Gardner and C. D. Dukes. Am. J. Obst. & Gynec. **69**:962-976 (May) 1955 [St. Louis].

Gardner states that microscopic examination of material from the majority of patients with bacterial vaginitis shows solid fields of small pleomorphic gram-negative bacilli. Vaginal material had been sporadically submitted to clinical laboratories for culture, but a logical correlation could never be drawn between the culture results and the stained smears, a point that suggested that the organism in the smears was not appearing in the cultures. Dukes studied material from a typical case of bacterial vaginitis. Although microscopic examination showed the characteristic organism in large numbers, no growth was obtained in culture mediums. In material from a second patient a large variety of highly enriched mediums was used, and incubations were made under various oxygen and carbon dioxide tensions. At the end of 48 hours, a 10% sheep blood agar plate, incubated under reduced oxygen tension, was found to contain thousands of minute transparent colonies that could be detected only by reflected light. A smear from these colonies showed bacilli similar to those seen on the direct smear. After finding the identical organism in pure culture in 13 of the next 14 patients considered as having bacterial vaginitis, it appeared that a specific etiological agent had been found to explain the majority of cases of "nonspecific" bacterial vaginitis. The authors assigned the name Hemophilus vaginalis to the newly isolated bacillus. Studies were made on 1,181 female patients. Sexually active women constituted the large majority of the patients but also included were a few children and postmenopausal women. The group included 602 obstetric and 579 gynecologic patients. Microscopic examinations of wet mounts and stained smears were made on patients with symptoms of vaginitis. All patients with an abnormal discharge, considered vaginal in origin, who showed no trichomonads or Monilia by microscopic examination, were subjected to bacteriological studies. Sixty-one of 80 patients with smears positive for trichomonads and 47 of 79 patients with moniliasis were also studied bacteriologically. Studies were also made on control groups. Of the 138 women in whom bacterial vaginitis was detected, 127 (92%) were attributed to Hemophilus vaginalis. The authors present proof of the pathogenicity of this organism and direct attention to the diagnostic character of certain epithelial cells designated "clue cells." H. vaginalis organisms isolated from 41 patients were tested against various antibiotics. The organism was found to be sensitive to bacitracin and to the tetracyclines. The tetracycline group was used for treatment in the early part of the study. When it was found that after treatment with the tetracyclines secondary infections with Monilia, Proteus, or micrococci (staphylococci) were found to be a frequent aftermath, resort was made to intravaginal triple sulfonamide (Ortho) cream. This triple sulfonamide effected cure in 10 of 13 patients. It has the advantage of not encouraging secondary infections. The necessity of the simultaneous treatment of husbands is stressed.

Endometriosis as Sequel of Genital Anomaly. L. Schmidt. Zentralbl. Gynäk. **77**:183-187 (No. 5) 1955 (In German) [Leipzig, Germany].

A 16-year-old girl experienced severe cramp-like pains in the right hypogastric region, as well as nausea and vomiting during her menstrual periods. In addition, and during the intermenstrual period, she had drawing pains in the right side of her abdomen. Examination indicated that her uterus was of normal size, but slightly displaced to the left. To the right of the uterus, a mass, the size of an apple, that, however, was not sensitive to pressure was palpated. A tumor of the uterine adnexa, possibly a dermoid cyst, was suspected, but operation revealed instead a duplication of the uterus. Whereas the uterus on the left side was connected with the vagina, that on the right side was closed at the level of the internal uterine os and was connected neither with the vagina nor with the left horn. The left ovary was normal, but the adnexa on the right side were buried in a conglomerate mass and covered by omentum. The right-sided duplicate uterus together with its attachments was removed. Examination of the surgical specimen revealed that the uterine tube had been transformed into a hydrosalpinx. Microscopic examination revealed endometriosis in the basal portions of the myometrium. An extensive endometriosis with old and more recent hemorrhages was found also between tube and omentum. In such a patient it may be difficult to decide whether the endometriosis is a sequel of the anomaly or an accidental concurrence. In the reported case normal menstrual bleeding from duplicate uterus

was impossible because of closure, and so it seems plausible that endometriosis was caused by stasis and reflux of the menstrual flow into the abdominal cavity (Sampson's implantation theory). The patient had a normal recovery.

Cesarean Hysterectomy. W. C. Bradbury. West. J. Surg. **63:** 232-244 (May) 1955 [Seattle, Wash.].

A review is made of 22,832 deliveries, of which 1,188 were by cesarean section. Among these, 84 cesarean hysterectomies were performed. There were no maternal deaths. A gradual increase in the percentage of cesarean sections, repeated cesarean sections, and cesarean hysterectomies was noted in the series. Cesarean hysterectomy proved to be a useful, and at times lifesaving, measure. The subtotal procedure is no more difficult to carry out than that done in the nonpregnant patient. Although it accomplishes the immediate need in any case, total cesarean hysterectomy is gradually replacing the subtotal operation. With modern equipment, good anesthesia, good assistance, and adequate training, the entire uterus can safely be removed at the time of cesarean section. Certain technical modifications of the nonpregnant procedure facilitate the total operation and produce better results. Stable patients approaching the menopause can safely be selected for cesarean hysterectomy as a means of sterilization when cesarean section and sterilization are indicated. Cesarean hysterectomy in younger patients should be limited to those with a primary indication for hysterectomy.

Use of Cortisone in the Prevention of Erythroblastosis in Infants of Rh-Sensitized Mothers. I. Dyer, R. C. Smith, J. Dent and others. Am. J. Obst. & Gynec. **69:**1083-1093 (May) 1955 [St. Louis].

Once a mother has produced an infant with the classical effects of Rh sensitivity, the chances are great that in subsequent pregnancies the infants will be equally affected and probably show greater depths of the hemolytic process. No reduction of maternal or infant sensitivity was noted with the use of ethinyl disulfonate or with haptens. Premature termination of pregnancy has not improved the fetal salvage. To the contrary, the prematurity thus induced complicates the management of an already complicated problem. Forty-five Rh-negative isoimmunized pregnant women, 40 of whom had previously produced babies affected by erythroblastosis, were given cortisone in the last trimester of pregnancy in an attempt to improve fetal survival. With meticulous control and selection of patients, the drug was well tolerated by both mother and baby. There was one major reaction in a mother, none in any infant. All reactions were reversible. There were 37 live babies, 8 stillbirths, and 5 neonatal deaths. Five liveborn babies were Rh negative. The over-all fetal mortality rate was 28.8% corrected to 15.5%, if two preventable deaths and four instances of inadequate therapy are deleted. The women studied represent a pregnant population of approximately 15,000. The over-all infant survival correlated with past obstetrical history and duration of drug therapy has not shown sufficient improvement to justify continued use of cortisone in treatment or prevention of erythroblastosis fetalis. The potent weapon in this problem still remains immediate exchange transfusion.

Combined Steroids to Suppress Lactation. P. W. Fiskio. GP **11:** 70-72 (May) 1955 [Kansas City, Mo.].

The authors administered Premarin (water-soluble conjugated equine estrogens) with methyltestosterone to 267 women to produce inhibition of lactation during the puerperium. The decision for suppression came from the patients themselves in 261 instances and was medically recommended in only 6. The dosage was three tablets every four hours for five doses, starting immediately on the patient's return to her room after delivery. Each tablet contained 1.25 mg. of the estrogens and 10 mg. of methyltestosterone. All patients were followed for at least six weeks after delivery. One hundred sixty-six patients (62.4%) who had no breast engorgement or untoward symptoms from the medication were considered to have had excellent results. Those who noticed a full but not painful sensation in the breasts were classified as having mild breast engorgement and were considered to have had good results; this category included 91 patients (33.8%). Ten patients (3.8%) with a full sensation and slight lactorrhea were classified as having moderate breast engorgement and were considered to have had only fair results. These symptoms occurred on the sixth or seventh day post partum. No patient was considered to have had poor results, since none had severe engorgement, recurrence of lactation, or untoward side-effects. Thus, the author considers his plan the method of choice in the suppression of lactation.

PEDIATRICS

Prophylaxis Against Group A Streptococci in Rheumatic Fever: The Use of Single Monthly Injections of Benzathine Penicillin G. G. H. Stollerman, J. H. Rusoff and I. Hirschfeld. New England J. Med. **252:**787-792 (May 12) 1955 [Boston].

Monthly injections of benzathine penicillin G were given to 145 patients with rheumatic fever in order to prevent recurrences. The patients ranged in age from 6 to 16 years and had had an attack of acute rheumatic fever within 18 months at the time prophylaxis was initiated. At each clinic visit (every four weeks) throat cultures were made, blood was obtained for determination of antistreptolysin O titer and erythrocyte sedimentation rate, and at six-month intervals electrocardiograms were obtained and fluoroscopy was performed. Patients who failed to keep a clinic appointment were seen within 48 hours by a visiting nurse, who administered benzathine penicillin and obtained throat swabs and blood specimens. In addition, the nurse investigated reported illness and made throat cultures when respiratory infection was encountered. A physician made a home visit when symptoms suggestive of rheumatic fever or a related complication were reported. Benzathine penicillin G was injected in a dose of 1,200,000 units contained in a volume of 2 cc. This dose was supplied in a disposable cartridge and was injected deeply into the upper outer quadrant of the buttock. Treatment was continued from September, 1952, to August, 1954. In addition to the outpatients treated, 265 patients hospitalized in the acute and convalescent stages of rheumatic fever received single monthly injections of 1,200,000 units of benzathine penicillin G. No recurrences of rheumatic fever were observed in the 145 patients who received monthly intramuscular injections of benzathine penicillin G, and only 4 patients gave evidence of recurrence of infection with group A streptococci during the period of study. Of 74 patients who had clinically apparent rheumatic heart disease on admission to the study, 8 were reclassified as having no heart disease at the end of the study when organic murmurs had disappeared and heart size had reverted to normal. Five additional patients showed improvement in cardiac status on the basis of the disappearance of an organic murmur or return of heart size to normal. Evidence of progression of heart disease appeared in only three patients, a new organic murmur appearing in two and progressive cardiac enlargement in the other. A total of 4,871 injections of benzathine penicillin G was administered to 410 patients. The average number of injections per patient was 12. Most patients experienced deep muscle soreness and tenderness that lasted for one to three days. This reaction was usually accepted without undue complaint. Only one patient dropped out of the study solely for this reason. Reactions assumed to be due to penicillin hypersensitivity occurred in five patients. The annual recurrence rate of rheumatic fever (in New York) was about 15% in the years 1936 to 1942, when antistreptococcic prophylaxis was not generally used. The annual rate of recurrence in patients who received either sulfadiazine or penicillin by mouth in other New York clinics was 2.3%, representing a decrease of 85%.The total absence of recurrences in the group treated with benzathine penicillin G may be significant, but an adequate comparison of the various forms of prophylaxis will require more extensive observations on larger numbers of patients. The daily oral administration of sulfonamides or penicillin has the disadvantage that patients are apt to forget to take their medication regularly, and for this reason monthly injections of 1,200,000 units of benzathine penicillin G afford a more reliable method of prophylaxis against recurrences of rheumatic fever.

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The Single Approach to Streptococcic Prophylaxis. R. A. Tidwell. Northwest Med. **54:**467-471 (May) 1955 [Seattle, Wash.].

Benzathine penicillin, a highly insoluble salt of penicillin, has been demonstrated as the most efficient agent for the production of penicillin blood levels that are required for the prophylaxis of respiratory infection by beta-hemolytic streptococci. This drug is now recognized as indispensable to the long-term management of patients with a history of rheumatic fever. Control of the Streptococcus has been achieved by giving one tablet or teaspoonful daily or one injection per month. This constitutes the "single approach" to streptococcic prophylaxis. Tidwell instituted such a prophylactic program in 1952, reporting observations on an initial group of 59 patients in *Northwest Medicine* (**54:**470 [May] 1954; abstracted in *J. A. M. A.*, **156:**87 [Sept. 4] 1954). One 200,000 unit tablet of benzathine penicillin was given daily. The present report is concerned with the continuation of the prophylactic program in 34 of the original 59 patients. This group includes 7 with congenital heart disease, 11 with rheumatic fever or rheumatic heart disease, one with asthma, 6 with recurrent respiratory infections, one with nephritis, and 7 siblings. One child, who, owing to an oversight, was not included in the program throughout the summer of 1953, had a strongly positive culture for beta-hemolytic streptococci, type X, on return. Despite the rather constant exposure of all the patients and the various intercurrent infections experienced by most, throat cultures taken at monthly intervals or less throughout the course remained consistently negative for beta-hemolytic streptococci except in two patients, in one of whom the organism temporarily appeared in the throat twice when medication was interrupted, and in one whose throat was cleared promptly by doubling the dose. The presence of tonsils did not interfere with effective prophylaxis. There was no recurrence of rheumatic fever, evidence of subacute bacterial endocarditis, or aggravation of renal disease or asthma in the children ill at the start of the program. No early or late suppurative or nonsuppurative sequelae followed any of the infections that occurred in this series. Benzathine penicillin was accepted willingly by all of the children. No evidence of hypersensitivity or drug resistance developed.

Control of Group A Streptococcal Infections and their Sequelae. L. W. Wannamaker. Journal-Lancet **75:**197-214 (May) 1955 [Minneapolis].

There no longer seems to be any reasonable doubt concerning the importance of group A streptococcic infections in the development of acute rheumatic fever and acute glomerulonephritis. In spite of this undeniable relationship, the pathogenesis of these diseases is still not clear. Variation in host response is well recognized but poorly understood. The antigen-antibody theory remains a fascinating hypothesis, but definite proof of its role in the pathogenesis of acute rheumatic fever or acute nephritis has not been produced; furthermore, the possible importance of bacterial hypersensitivity is not known. Recent studies have attracted attention to the significance of strain variation in causing acute glomerulonephritis and to the importance of the persistence of the infecting Streptococcus in the pathogenesis of acute rheumatic fever. At present, the control of the two diseases can best be accomplished through the control of acute streptococcic infections. Adequate treatment of these infections with penicillin prevents acute rheumatic fever and probably reduces the incidence of acute glomerulonephritis. For therapy to be adequate, the organism must be eradicated. This seems to depend primarily on the length of time treatment is continued. Continuous prophylaxis with either sulfadiazine or penicillin prevents rheumatic recurrences by preventing streptococcic infection. Prophylaxis should be continued as long as risk of infection or cardiac damage is great. Complete control of streptococcic infections and their sequelae cannot be expected from the use of antimicrobial agents. The difficulties of differential diagnosis of upper respiratory infections and the frequency of subclinical and atypical streptococcic infections make this impossible. In addition, the long-term effects of the repeated use of these agents are not known. Further advances in the prevention of these diseases will depend on additional knowledge of their pathogenesis and continued inquiry into modes of spread and immunizing methods.

Chlorpromazine in the Control of Vomiting in Children: Preliminary Clinical Evaluation. C. W. Daeschner, J. L. Clark, G. Y. George and R. A. Frankel. A. M. A. Am. J. Dis. Child. **89:**525-530 (May) 1955 [Chicago].

Chlorpromazine hydrochloride will control vomiting in adults. The studies described in this paper were concerned with ascertaining effective dosage schedules for children, evaluating therapeutic efficacy, and observing side-effects. During 18 months, 100 clinical trials of chlorpromazine were carried out in infants and children, ranging in age from 6 weeks to 14 years, the majority being under 5 years. Vomiting was caused in 64 of the children by gastroenteritis either nonspecific or associated with acute infections. Other causes were: chalasia of the esophagus, ketogenic diet, diabetes mellitus with acidosis, irradiation therapy for such conditions as leukemia, lymphosarcoma or other malignancies, chemical gastritis due to acetylsalicylic acid therapy, pyloric stenosis, terminal osteosarcoma, postacute bulbar poliomyelitis, appendicitis, and encephalitis. The chlorpromazine was given intramuscularly, by mouth, or in the form of suppositories. Some patients were treated with more than one dosage schedule in an effort to determine the most effective dose range. The intramuscular injections consisted of a solution in isotonic sodium chloride solution ranging in concentration from 1 to 5 mg. per cubic centimeter. The syrup contained 2.5 mg. per cubic centimeter (10 mg. per 4 cc.), and the tablets contained 5, 10, or 25 mg., depending on the dose desired. The suppositories contained from 25 to 50 mg. In 83 of the patients the response was excellent or good. In an additional nine there was a decrease in the vomiting, but the role of chlorpromazine was not definite. In eight patients no clinical improvement was noted. Although toxicity was not a significant factor, since chlorpromazine is a new drug the following precautions should be observed: (1) in patients receiving the drug for more than a few days the possibility of agranulocytosis should be considered; (2) it would seem injudicious to treat patients known to have liver disease or jaundice with chlorpromazine, and the drug should be discontinued in any patient in whom jaundice appears; (3) a helpful soporific effect is a common companion of effective chlorpromazine therapy; pharmacological studies have shown that when chlorpromazine is given concomitantly with central-nervous-system-depressants it may potentiate their effect; and (4) the cause of vomiting should be determined prior to therapy with chlorpromazine, since the latter may mask diagnostic or prognostic signs and symptoms. Its use as an antiemetic in central-nervous-system injury or intestinal obstruction is debatable. Chlorpromazine is an effective antiemetic agent for the symptomatic control of vomiting in children. It appears to have a wide range of usefulness.

Use of Cobalt in Some Common Anemias of Childhood. B. L. Coles. Arch. Dis. Childhood **30:**121-126 (April) 1955 [London, England].

In view of the unsatisfactory response to iron of certain common anemias in childhood, a series of patients was treated with cobalt to see whether this substance would prove a satisfactory substitute for iron in refractory cases. Fifty children were treated, and all had types of anemia usually showing a poor response to iron, liver, and other hemopoietic agents. There were 31 children in whom anemia was associated with infection; 10 were anemic premature infants; and three were infants with Rh incompatibility, who showed a residual anemia in spite of transfusions. One patient had severe physiological anemia, and in one anemia developed after Ramstedt's operation, although there was no evidence of gastric hemorrhage. The remaining patients comprised twins with a fairly severe anemia of unknown etiology and a patient with erythrogenesis imperfecta. This last patient was the only one who failed to respond to cobalt therapy. Cobalt sulfate was given by mouth in daily doses of 20 or 25 mg. Treatment was generally continued for about three weeks. No toxic effects were observed with these doses. In an effort to

elucidate the still unknown mode of action of cobalt therapy in anemia, marrow punctures were made in 12 children before and after treatment. In six of these anemia was associated with infection and six were premature infants. All 12 responded satisfactorily as far the the peripheral blood was concerned. Nine showed a rise in the total erythroid precursors in the marrow, associated with a fall in the myeloid/erythroid ratio. Erythroid marrow hyperplasia suggests that one action of cobalt is a direct stimulation of the marrow erythroid tissue. Similar changes in the erythroid tissue have been observed by others who used cobalt in anemia. The reticulocyte response to cobalt was not dramatic.

Technical Note on Intrafunicular Transfusion in Treatment of Asphyctic Shock of Newborn Infant. G. Ferraris. Minerva ginec. **7**:312-315 (April 15) 1955 (In Italian) [Turin, Italy].

Transfusion into the umbilical vein of newborn infants with severe asphyxia aims at checking the vascular hemodynamic imbalance, which is believed to be the main cause of the shock that accompanies this condition. The standard procedures used in the resuscitation of the newborn infant—aspiration of the respiratory pathways, heating, and administration of oxygen—are also carried out concurrently. At the University of Perugia these procedures are carried out by four trained and experienced persons who work as a team and who can be ready to start in less than one minute after the delivery. A no. 9 catheter, 14 to 16 cm. in length, is threaded through the umbilical vein, and the blood-containing syringe is connected to the other end of the catheter. The average quantity of blood administered varies from 30 to 60 cc., according to the infant's weight, muscle tone, cardiovascular condition, and quantity of blood lost. Immediately after the transfusion of a few cubic centimeters of blood, a sudden improvement in the general condition is observed together with the first respiratory movements. This sudden improvement has been ascribed to stimulation of particular vascular reflexes or a direct mechanical action in the blood stream.

Ophthalmia Neonatorum. H. L. Ormsby. Canad. M. A. J. **72:** 576-580.(April 15) 1955 [Toronto, Canada].

In a study of 8,418 newborn infants there were three cases of gonococcic ophthalmia among 1,703 receiving two drops of Sulmefrin solution in each eye at birth, one among 3,125 receiving one drop of 1% silver nitrate solution, and none among 1,570 receiving one application of 10% sodium sulfacetamide ointment. Among 2,020 infants receiving no prophylaxis at birth there were five cases of gonococcic ophthalmia. Mild chemical conjunctivitis was seen in most infants receiving 1% silver nitrate prophylaxis. This cleared within 48 hours, and no other sequelae were observed. Inclusion conjunctivitis occurred in each series and did not appear to be influenced by any of the prophylactics. All cases of this disease ran a benign course, and many cleared spontaneously without treatment. The intramuscular injection of penicillin into the mother during labor would seem to be the best prophylaxis of gonococcic ophthalmia in the infant, but the danger of hypersensitivity reactions prohibits routine use of this method. The same difficulty applies to treatment of the infant with intramuscularly administered penicillin. It is concluded that, although certain new areas of therapy, such as the use of prophylactic agents in ointment base, are worthy of study, the time-tested procedure of applying 1% silver nitrate solution to the conjunctival sac at birth is an efficient prophylactic against gonococcic ophthalmia.

Nephrosis and ACTH: Special Reference to Humoral Changes Observed in Four Cases. J. Meneghello R. and F. Monckeberg B. Rev. chil. pediat. **26:**1-8 (Jan.) 1955 (In Spanish) [Santiago, Chile].

Four patients between the ages of 1 and 4 years with nephrosis of from two to six months' duration were observed. All patients had intense edema, anasarca, ascites, and marked albuminuria. The serum proteins were low with decreased albumins and increased alpha and beta globulins. The serum cholesterol was increased. Hematuria was found in three patients. ACTH was given intravenously in doses of 7 to 15 mg. at intervals of 12 hours for about 10 days. In the course of treatment the intake of salt was restricted and penicillin or chloramphenicol was administered. All patients responded with an abundant diuresis, a great loss of body weight, complete disappearance of edema and albuminuria, absence of sodium retention in urine, elimination of sodium and potassium in the urine in normal ratio, conversion of the changes of serum proteins into normal patterns, and control of all the other humoral derangements and clinical symptoms of nephrosis. The complications observed included transient moderate uremia in all patients, moderate hypertension in some, and hypertension with cardiac insufficiency that made discontinuation of the treatment necessary in one patient. Marked natremia occurred during intense diuresis in one patient, and it was controlled by administration of sodium. Remission lasted for three and six months, respectively, in two patients. In the other two patients follow-up observations were not made. Although the response to the intravenous use of ACTH is prompt and satisfactory, the treatment should not be used as a routine. It is indicated for hospitalized patients and for patients who respond to the intramuscular treatment with a poor diuresis. The treatment may be discontinued as soon as an abundant diuresis appears. The normalization of humoral changes after ACTH diuresis observed by the authors suggests that ACTH controls the hydrosaline imbalance that is the primary cause of all humoral derangements and clinical symptoms of nephrosis.

OPHTHALMOLOGY

Macular Holes in Retinal Separations: Their Significance and Their Surgery. A. H. Keeney. Am. J. Ophth. **39:**648-653 (May) 1955 [Chicago].

Macular holes are due to contusion or degeneration but in either event cystic degenerative changes precede the typical hole formation. Simple, degenerative holes do not lead to retinal separation. Proper retinal position is maintained in the presence of typical, punched-out lesions when: (1) the hole is a cyst with an intact inner wall; (2) such a macular cyst has ruptured through its inner wall only, thus leaving an intact outer wall; or (3) perimacular adhesions between the choroid and retina have been created by local inflammation. Macular holes are rarely the cause of retinal separation, in which case they must be complete holes. More commonly they are incomplete and incidental to the pathogenesis of separation. When macular holes are incomplete they should not be subjected to operation with its attendant loss of valuable perimacular acuity. Sealing of complete macular breaks should be done with small, partial-penetrating electrodes using low current, directed precisely to the edges of the hole.

Hereditary Degeneration of the Macula Occurring in Five Generations. C. T. Davis and R. W. Hollenhorst. Am. J. Ophth. **39:**637-643 (May) 1955 [Chicago].

Degeneration of the macula of each eye was discovered in 24 persons in a kinship of 148 members, belonging to five generations. This family was discovered when two young women, 29-year-old first cousins, presented themselves for examination at the Mayo Clinic because of pregressive loss of visual acuity in each eye since early childhood. The visual defects in each of these two young women were identical. As they were questioned, the existence of many similar visual defects among their kin was disclosed. Since virtually the entire family resided in central Wisconsin, it was possible to make a complete genetic study. A macular lesion was responsible for the visual disability observed among members of this family. The lesions found in the maculas of persons of about the same age were almost identical in appearance, and the patients' complaints were similar. The age at onset of manifest visual disability varied from early childhood to adolescence. The lesions were progressive and were symmetrical in each eye. A central scotoma was responsible for the impairment of vision. Marked impairment of color discrimination was associated with the lesions. Each patient had some degree of day blindness, but none had an

associated cerebral lesion. The authors believe that the course of the disease, the appearance of the lesions ophthalmoscopically, and the other findings in the ocular examination place the disease in the group of heredofamilial degenerations of the macula without cerebral involvement; that is, Sorsby's macular dystrophy. The defect is transmitted as a dominant trait with complete penetrance.

Laboratory Observations on the Ocular Use of Tetracycline. J. W. Hallett, K. Naib and I. H. Leopold. Am. J. Ophth. **39:**691-696 (May) 1955 [Chicago].

It has been claimed that tetracycline, chlortetracycline, and oxytetracycline have the same broad-spectrum activity against gram-negative and gram-positive bacteria, certain viruses, and rickettsial infections. Solutions of tetracycline in 0.85% sodium chloride maintained their antibacterial activity undiminished after three weeks' storage at 5 C, whereas similar preparations of chlortetracycline and oxytetracycline commenced to deteriorate after from 24 hours to one week of storage. Furthermore tetracycline is said to diffuse readily into body tissues and fluids and to have low toxicity and a wide margin of safety. Since no reports were available on the ocular effects of tetracycline, studies were made on the eyes of rabbits. Summarizing the results of these studies, the authors say that aqueous levels theoretically effective against gram-positive organisms appear up to two hours after intravenous injections of 100 to 150 mg. in rabbits. Small corneal and smaller vitreous levels are found one hour after intravenous injection of 150 mg. The latter dose may, however, be nearly lethal. Subconjunctival injections of 10 mg. per cc. produce adequate corneal and aqueous levels up to four hours and vitreous levels up to one hour. The inflamed eye accepts the antibiotic in larger amounts than does the normal eye. Corneal bath or eye drops in concentrations of 25 mg. per cubic centimeter produce effective corneal levels for four hours. Aqueous levels are adequate up to two hours in the intact and up to four hours in the inflamed eye. Subconjunctival injections in concentrations up to 5 mg. per cubic centimeter are safe; eye drops in concentrations up to 25 mg. per cubic centimeter are harmless; corneal baths in concentrations up to 10 mg. per cubic centimeter are innocuous; and intracameral injections in concentrations greater than 1 mg. per cubic centimeter are dangerous.

Increase in Optic Nerve Lesions in Patients with Tuberculous Meningitis Being Treated with Isoniazid and Streptomycin. G. Janssen and W. Böke. Klin. Wchnschr. **33:**477-479 (May 15) 1955 (In German) [Berlin, Germany].

Studies on 245 children with tuberculous meningitis who were treated between 1948 and 1954 revealed that in those admitted for treatment since the introduction of isoniazid therapy in the second half of 1952, there was a definite increase in optic nerve lesions. Papillary changes taking the form of edematous swelling may correspond to choked disk or optic neuritis, differentiation being possible only by functional tests on the visual acuity and visual fields, which are rarely possible in a patient with severe meningitis, the less so if the patient is a child. When functional tests were possible, signs of optic neuritis were detected, and the temporal atrophies observed in several patients also suggested neuritic processes. Vascular lesions leading to prolonged ischemia may be brought on by perioptic meningitis or by optochiasmatic arachnitis, and rarely a miliary tubercle within the optic nerve may cause a papillitis. Estimates on the incidence of such lesions in tuberculous meningitis vary widely, but the authors believe that the increase in optic nerve lesions and the progression of these lesions to optic atrophy since 1952 must be due to a new factor. Since there is no evidence that the combination of isoniazid and streptomycin is particularly toxic, the authors believe that perhaps the giving of massive doses at the onset is responsible. For this reason they now dispense with the intrathecal administration of isoniazid at the onset, the more so, since with adequate oral doses, isoniazid is known to penetrate into the cerebrospinal fluid.

THERAPEUTICS

A New Antihistamine for Treatment of Various Allergic Manifestations. N. W. Clein. Ann. Allergy **13:**163-168 (March-April) 1955 [Minneapolis].

A new antihistamine, 1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine tartrate (Sandostene), was given to 124 patients with hay fever due to pollen grass and other forms of allergy. The new drug was given alone and in combination with calcium, orally and intravenously, from May through August. All patients under 6 years of age were treated with the syrup of the antihistamine combined with calcium, and all patients over 6 were given the antihistamine in 25 mg. tablets. The average dose of the syrup was one teaspoonful three or four times a day. Two to four tablets daily were given depending on the age of the patient and the severity of the symptoms. One week the average dose was given, followed by one week of rest, and the third week the dose was doubled. Of the 124 patients, 76 had hay fever, 12 hay fever and asthma, 17 eczema, 8 perennial allergic rhinitis, 4 urticaria, and 7 angioneuritic edema with urticaria. The last seven patients were given intravenous injections of Sandostene combined with calcium in doses of 10 cc. The antihistamine was given only to those whose symptoms were not relieved by the grass pollen antigens and other treatment. A group of patients with similar symptoms was used as control. Of the 124 patients, 21 obtained excellent, 38 good, 35 fair, and 30 poor results. Two children had minor toxic manifestations. The best results were obtained in smaller children and in those whose symptoms were caused primarily by inhalants rather than foods. There were no cases of drowsiness, and the author was particularly impressed with the lack of undesirable side-effects. Since this new antihistamine is available in tablet form, in syrup, and in ampules containing the product combined with calcium, the form most suitable for each patient can be chosen. The combination with calcium in syrup and ampules results in a potentiation of the effect on cellular and vascular permeability. Although the new antihistamine, which appears to be more effective than others, is a valuable adjunct in the treatment of various allergic manifestations, specific allergic management is still of primary importance in the control of allergic disease.

The Question of Reactions to Mercurial Diuretics: A Reappraisal. E. A. Brown. Ann. Allergy **13:**131-159 (March-April) 1955 [Minneapolis].

The advent of the newer organic mercurial diuretics, given intramuscularly, subcutaneously, or orally, the increased caution in making dosage schedules, and the awareness of the implications of early minor undesirable side-effects have reduced the number of fatal reactions more than one would expect on the basis of idiosyncrasy to such commonly used drugs. In one clinic 13,000 injections of mercurial diuretics have been given in a four-year period, without any ill effects. One of the author's own patients received weekly injections for more than 10 years, with no adverse effects. When the physician is alert to problems of dosage in relation to the patient's age and weight, to water and electrolyte balance, to side-effects as evidenced by excessive diuresis, and to the possibility of allergic reactions, toxic effects due to large doses should easily be avoided. The small group of truly allergic patients can be recognized and treated with the proper precautions. The history will, if directed towards discovering "drug-reactors," help uncover those who require special handling. Treatment should always be initiated with small doses of 0.2 to 0.5 cc. Intradermal skin tests and patch tests, even on abraded skin, are not dependable. The injection of 0.05 cc. of serum from a patient taking the mercurial diuretic in question (and not sensitive to it) injected intradermally will often result in a wheal, if the recipient is sensitive to the drug. Since normal serum evokes a slight to moderate response, good technique must be used and the results interpreted qualitatively as well as quantitatively. A positive reaction to the test does not mean that the patient cannot tolerate with safety another mercurial diuretic, especially if the same precautions are followed. Choice of a diuretic agent may be directed to different classes of compounds, as well as to different drugs within each

class. The routes of administration constitute another basis for choice. Mercurial diuretics are remarkably safe drugs when properly used. Such use, however, requires a recognition of the fact that the patient who needs them presents a dynamic system involving the interplay of a number of physiological and pathological processes, all of which must be taken into account for the maximum safety.

Treatment of Leukemia and Allied Disorders with 6-Mercaptopurine. J. R. Fountain. Brit. M. J. **1:**1119-1124 (May 7) 1955 [London, England].

Of 26 patients with leukemia and allied diseases treated with 6-mercaptopurine, a purine antagonist, at the General Infirmary in Leeds, England, since June, 1953, 13 had acute leukemia, 7 chronic myeloid leukemia, 2 chronic lymphatic leukemia, 2 multiple myeloma, one mycosis fungoides, and one erythroderma secondary to an underlying reticulosis of undetermined type. The dose of the drug was based on that suggested by Burchenal, the initial dose being about 2.5 mg. per kilogram of body weight. Thus a 5-year-old child was started on 50 mg. and an adult on 150 to 200 mg. per day. The same dosage scheme was used both for patients with acute and those with chronic leukemia, and in all patients, the daily amount was divided in doses of 25 or 50 mg. given over 24 hours. Seven of the 13 patients with acute leukemia responded to the treatment: 5 had complete clinical and hematological remissions, and 2 had partial remissions. The remissions were only temporary, and resistance to further therapy with 6-mercaptopurine eventually resulted. Of the seven patients with chronic myeloid leukemia, one died of cerebral thrombosis a week after treatment was instituted. The other six patients showed a varying response, with increase in well-being, activity, appetite, and weight in four, and diminution in the size of the spleen and lymph nodes in five. The leukocyte count fell in all six patients, and erythropoiesis improved in two. One patient in the acute terminal phase had a remission lasting four and a half months. The two patients with chronic lymphatic leukemia, the two with multiple myeloma, and the patient with reticulosis of the skin did not respond to the treatment, but the patient who had mycosis fungoides obtained some improvement. Six-mercaptopurine is of low toxicity, and no serious complications followed its use. Whether patients who have a complete remission should receive a daily maintenance dose of 6-mercaptopurine remains to be answered, but from the author's limited observations it seems likely that maintenance therapy may not greatly prolong the remission. Continuous therapy seems essential in chronic myeloid leukemia if the beneficial effect of the drug is to be maintained. One of the patients was symptom-free and fully active for six months on a daily maintenance dose of 50 or 100 mg. In the absence of maintenance treatment a clinical and hematological relapse may follow the discontinuation of the drug within a month. With the knowledge that 4-aminopteroyl glutamic acid (aminopterin) and amethopterin, corticotropin and cortisone, and 6-mercaptopurine may all produce clinical and hematological remissions in acute leukemia, it seems desirable to give patients the advantage of such chemotherapy; sequential use of these drugs may offer several months of useful life. Although more patients with chronic myeloid leukemia must be treated before the ultimate value of 6-mercaptopurine is known, the initial observations suggest that it will have its place in the management of this disease.

Malarial Therapy in the Nephrotic Syndrome. O. G. Shaper. Brit. M. J. **1:**1132-1135 (May 7) 1955 [London, England].

Four men and three women between the ages of 18 and 52 years with the nephrotic syndrome, i. e., with edema, proteinuria, and hypoalbuminemia, but without hypertension, nitrogen retention, or electrolytic disorder, and without an appreciable number of red blood cells in the urine, were given malaria therapy at the tropical disease center of the Sefton General Hospital, in Liverpool, England. The patients had failed to respond to more conservative forms of treatment. Six of the seven patients were infected with Plasmodium vivax by intravenous inoculation, and one patient was infected with Plasmodium ovale. The patients were allowed to have as many chills as they were capable of withstanding. Three of the seven nephrotic patients had a pronounced remission of symptoms for one year. The improvement in two other patients could not be associated with the malaria therapy. The last two patients died of their basic condition, but, as they were both severely ill and the malarial paroxysms were poor or curtailed in number, it would be unfair to say that malaria therapy had failed. The satisfactory results obtained in three patients encourage the continued use of malaria treatment in nephrotic patients who do not respond to more conservative treatment.

Toxic Hepatosis with the Aspect of Intrahepatic Obstructive-Type Jaundice After Administration of Chlorpromazine (Largactil), Atophan, Arsphenamine and Methyltestosterone. C. Maier and J. R. Rüttner. Schweiz. med. Wchnschr. **85:**445-448 (May 7) 1955. (In German) [Basel, Switzerland].

The occurrence of jaundice after the administration of chlorpromazine (Largactil) is described in two psychotic women, aged 30 and 83 respectively. The total dose of chlorpromazine given to the first patient was 1.8 gm., and that given to the second patient was 2.5 gm. The clinical aspect of the younger woman corresponded with that of obstructive jaundice in three patients reported on by Van Ommen and Brown (*J. A. M. A.* **157:**321 [Jan. 22] 1955). The 83-year-old patient died of pneumonia and cardiac decompensation and autopsy revealed cirrhosis of the liver associated with icterus. A toxic hepatosis resulted from the administration of chlorpromazine in the first patient, while in the second patient cirrhosis of the liver was imminent but was not recognized when chlorpromazine was administered. The occurrence of obstructive jaundice after the administration of other drugs such as phenylquinoline carboxylic acid (Atophan-Cinchophen), arsphenamine, and methyltestosterone has been reported in the literature. The various observations of chlorpromazine-induced icterus suggest caution in the administration of the drug to psychiatric patients. Biliary stasis as a possible untoward reaction to the drug should not be considered harmless. Evaluation of the degree of severity of the chlorpromazine-induced icterus should not be based on the result of the protein flocculation or galactose tests, but on prothrombin time, alkali phosphatase level, and cholesterol. The daily maximal dose of the drug should be reexamined by the psychiatrists.

Serum Penicillin Concentration After Peroral Administration of Penicillin Combinations With and Without Probenecid. K. Lind and C. Trolle-Lassen. Ugeskr. læger **117:**519-522 (April 28) 1955 (In Danish) [Copenhagen, Denmark].

The main investigations were carried out in well persons of two age groups, 20 to 25 and 68 to 78. It was found that dibenzylethylendiamidinedipenicillin (DBED) by the mouth does not offer any therapeutic advantage over ordinary benzyl penicillin. A certain therapeutic effect is ascribed to the high initial serum concentration of benzyl penicillin. Simultaneous peroral administration of these penicillin combinations and probenecid gives a longer lasting therapeutic serum penicillin concentration than the administration of penicillin alone, so that oral administration every eight hours seems to suffice. The older age group showed a higher and longer lasting serum penicillin concentration than the younger age group, which is explained by reduction of renal function due to age.

A Year's Clinical Experience with Spiramycin in Infectious Diseases. A. Darbon and R. Crosnier. Presse méd. **63:**681-683 (May 7) 1955 (In French) [Paris, France].

The new antibiotic, spiramycin, was recently extracted from Streptomyces ambofaciens. The authors used it on about 100 patients. Spiramycin has good therapeutic activity on gram-positive organisms. Its activity was as good as, and sometimes better than, that of the better-known antibiotics. It was excellently tolerated and was definitely superior in this respect to other antibiotics as far as oral administration was concerned. Only

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one patient had a gastrointestinal reaction. The daily doses were of 2, 3, and sometimes 4 gm.; the 3-gm. dose appeared to be the best. There was a certain amount of disparity between the drug's activity in vitro and in vivo. In two patients, spiramycin proved more efficient than could have been expected, judging from laboratory tests, and in a third, the drug's efficacy was disappointing compared to what was seen in vitro.

Use of Zetacillina in Surgical Infections. M. Rubino. Clinica **15:**221-223 (No. 4) 1954 (In Italian) [Bologna, Italy].

"Zetacillina," a drug in which penicillin is combined with a sulfonamide, was used in the treatment of 27 patients with surgical infections. From 6 to 12 capsules, each containing 75,000 units of penicillin and 0.25 gm. of the sulfonamide, were given to the patients daily for varying lengths of time. The drug benefited most of the patients. The results were good in 20, mediocre in 5, and poor in 2. The use of this drug is contraindicated in conditions in which the intestinal absorption is altered, in the immediate postoperative course, and in intestinal occlusions, because in such instances therapy should be given by the parenteral route.

PATHOLOGY

Pathology of Cerebral Palsy: II. Cerebral Palsy Due to Encephaloclastic Processes. A. Towbin. A. M. A. Arch. Path. **59:**529-552 (May) 1955 [Chicago].

Twenty-three cases of cerebral palsy, derived mainly from the population of the Columbus State School, Ohio, between 1950 and 1954, were studied at autopsy by Towbin. Three basic pathological types were evident in this group. Developmental defects of the brain accounted for the neurological disorder in six patients who were reported on in a previous paper (abstracted, *J. A. M. A.* **158:**888 [July 9] 1955). Of the other 17, antecedent systemic disorders, such as neonatal anoxia and erythroblastosis fetalis, were considered to be the mechanism of damage in 8; cerebral palsy was caused by mechanical injury to the brain, hydrocephalus, and other intrinsic local defects of the brain in 9 cases. Cerebral palsy is the result of a heterogeneous group of pathological processes. The lesions of the brain in this disorder are incurred during fetal and infantile life; in most cases the pyramidal or extrapyramidal system is involved. Only by correlating clinical observations with the findings in the brain at autopsy can a comprehensive appraisal of the processes in cerebral palsy be obtained. Further resolution of the problem of causation in cerebral palsy is of immediate importance as a requisite to the successful pursuit of prophylaxis and treatment. It is increasingly evident that cerebral palsy in a significant proportion of cases is related to systemic disorders of the fetus and infant. Consequently, the problem of cerebral palsy becomes increasingly the province of the general pathologist.

Antibody Production by Spleen in Vitro: I. Influence of Cortisone and Other Chemicals: II. Correlation of Weight of Rabbit, Weight of Spleen, and Level of Antibody Produced in Vitro. I. M. Mountain. J. Immunol. **74:**270-277 and 278-280 (April) 1955 [Baltimore].

The production of H-agglutinin in vitro by spleen taken from rabbits immunized with typhoid vaccine was studied. Spleens removed from the animals four days after a single intravenous injection of vaccine were minced, and a culture of minced spleen served as the basis for the author's test system. Antibody production in culture continued for at least three days. The reproducibility of the test system was evaluated statistically in order to assay the effect of the addition of various inorganic and organic chemicals, including vitamins and hormones, on antibody production. Antibody formation in vitro required oxygen and was suppressed by sodium cyanide in final concentrations of from 10^{-2}M to 10^{-4}M, and by salts of the heavy metals at minimal concentrations indicated: manganous sulfate 10^{-3}M, ferric chloride 10^{-5}M, and cupric sulfate 10^{-4}M. Antibody formation in vitro was also suppressed in the presence of 100 mM. sucrose, by the "essential" amino acids at 30 mM. (combined total concentration) and by the reducing substances: reduced glutathione in a concentration as low as 15 mM., cysteine in a concentration of 15 mM. or lower, ascorbic acid in a concentration of 15 mM. or lower, as well as by cortisone in a concentration of 32 mg. per 100 cc. or more. With the exception of glutathione, and possibly sucrose, none of these substances, at concentrations that were found to be inhibiting, altered the antibody titer when incubated with immune serum. Thus the various chemicals inhibited some phase of antibody formation by surviving cells in culture rather than by destruction of antibody once formed. Eleven rabbits of weights varying from 3 to 6 kg. were each given a single intravenous injection of typhoid vaccine. Four days later the rabbits were bled from the heart with the aid of pentobarbital anesthesia and the entire spleen was removed. The weight of the spleen and the weight of the rabbit showed a positive correlation. Furthermore the weight of the spleen, as well as the weight of the rabbit, showed a positive correlation with an index of the antibody-forming capacity of a given mass of the spleen in vitro. These results indicate that in selecting animals for study of antibody production in vitro not only will a heavier spleen be obtained from a larger animal but a given fragment of such an antibody-producing tissue can be expected to give a higher yield of antibody. The observed correlation between the size of the spleen and its capacity (per unit weight) to produce antibody introduces a new parameter for the study of the cells responsible for antibody production.

RADIOLOGY

Physiological Aspects of the Tumoral Circulation Proper in Ten Cases of Glioblastoma Multiforme. V. A. Fasano and G. Broggi. Minerva chir. **10:**215-219 (March 15) 1955 (In Italian) [Turin, Italy].

Ten patients with glioblastoma multiforme were studied by angiography. In most of these patients the angiograms revealed a direct arteriovenous communication. The presence of a neoplasm, through which these communications were seen, modified the cerebral hemodynamics. The result was slackening of the cerebral circulation, the extent of which depended on the morphological aspect of the neoplastic vascular network. This altered circulation became more evident on the angiograms that showed the circulation within the neoplasm. In some of these patients the angiograms failed to demonstrate a vascular system within the glioblastoma. Histological studies of the removed tumors seemed to indicate that this failure occurs more frequently in patients in whom such changes as hemorrhage, necrosis, vascular proliferation, or cysts are present within the neoplastic tissue.

New Agents for Cholecystangiography (Telepaque, Biligrafin). T. Denstad. Tidsskr. norske lægefor. **75:**259-263 (April 15) 1955 (In Norwegian) [Oslo, Norway].

The new agents for cholecystography, Telepaque for peroral use and Biligrafin for intravenous use, have been tested in Aker Hospital for about a year. They contain three atoms of iodine in the molecule, give a denser gallbladder shadow, and allow roentgenologic presentation of the bile ducts. With Telepaque this depends on a functioning gallbladder that can concentrate the bile containing the contrast medium, but the bile ducts can be filled with the contrast medium even though the gallbladder has been removed or its concentration ability is reduced (cholecystitis) if Biligrafin is used. Besides the detection of stones in the common bile duct study of the bile duct dyskinesias is made possible. For examination especially of the bile ducts Biligrafin should be applied, while Telepaque affords better information about the condition of the gallbladder. Side-effects are few. Grave liver affection, marked jaundice (but not slight jaundice), acute nephritis, uremia, and gastrointestinal disturbances are contraindications.

QUERIES AND MINOR NOTES

PERNICIOUS ANEMIA

TO THE EDITOR:—*I am interested in pernicious anemia and would like information especially as to the length of time a patient may have the disease before proper diagnosis or sufficient symptoms appear to make such a diagnosis.*

M.D., New Jersey.

ANSWER.—Pernicious anemia, with or without neurological component, is a manifestation of vitamin B_{12} deficiency. Irreversible gastric atrophy and achylia gastrica are constant findings. The disease usually results from decrease of the intrinsic factor of normal gastric juice. This substance, which is perhaps a mucoprotein, specifically facilitates the difficult absorption of dietary vitamin B_{12}. Any derangement of the balance of intrinsic factor secretion, vitamin B_{12} intake, and intestinal absorption may in time result in vitamin B_{12} deficiency. Probably about 1 mcg. of vitamin B_{12} must be assimilated daily for health. The interval required for this deficiency state to develop depends on the degree of failure of absorption and in addition on the total body store of vitamin B_{12} and its rate of depletion. Following total gastrectomy this may require two or three years. In most instances of the spontaneous disease the duration of symptoms is of the order of 6 to 12 months. However, among patients with pernicious anemia in remission many may not experience signs or symptoms of relapse until two or more years after therapy has been stopped. Early diagnosis depends on further studies that are indicated by the persistence of commonplace gastrointestinal (glossitis, anorexia, "gas") and/or suggestive neurological (symmetrical paresthesias or ataxia) symptoms. Absence of such symptoms in a third of the patients or failure to recognize their significance in others can easily lead to overlooking the relatively subtle early changes in peripheral blood or bone marrow until the anemia has become severe or spinal cord lesions disabling. It must be appreciated that, without the characteristic symptoms and without at least a hemoglobin determination and inspection of a blood smear, patients with pernicious anemia may pass for months as having hypochondriasis, heart trouble, chronic indigestion, or even flat feet. Until the diagnosis of pernicious anemia has been definitely excluded, it is important not to obscure the blood picture further nor possibly to accelerate the progress of spinal cord disease by the oral use of folic acid or of vitamin mixtures containing this vitamin. When the diagnosis of pernicious anemia is established, the parenteral injection of 30 mcg. of vitamin B_{12} either as such or as liver injection U. S. P. should be initiated at weekly intervals. After one or two months similar injections at monthly intervals are adequate maintenance therapy.

HYPERTENSION

TO THE EDITOR:—*Please provide information on the latest methods for treating somewhat severe cases of hypertension that are not yet definitely malignant. How about Hyphex?*

Joseph M. Koreen, M.D., Wilmington, N. C.

ANSWER.—Hyphex is a term occasionally applied to the use of hexamethonium chloride and hydralazine hydrochloride orally for patients with hypertension. Of the two drugs, hexamethonium is best established as capable of reducing blood pressure. The dose must be individualized, slowly increased to an amount between 1 and 4, usually 2 to 3 gm. daily. Tablets contain 250 mg. of the salt and should be given 1 to 4 at a time on an empty stomach, a half hour before meals and at bedtime. Constipation usually occurs and requires laxatives or cathartics. Ileus must be avoided. Patients should be instructed to skip doses when hypotension or weakness occurs. They should be cautioned about the hazard of fainting while standing still at times when postural hypotension is marked. Hydralazine when used alone only occasionally reduces blood pressure. Some authorities favor use of hydralazine in amounts varying from 200 to 600 mg. a day only as a supplement to hexamethonium. Since hydralazine causes a syndrome resembling rheumatoid arthritis or systemic lupus erythematosus in 4 to 13% of patients, many physicians prefer use of some other drug. A good program of treatment would be the trial of hexamethonium alone orally increasing to the tolerated full therapeutic dose. Use of any second drug might then be tried if necessary.

TRANSMISSION OF PARASITES FROM DOGS

TO THE EDITOR:—*What parasites can be contracted from dogs?*

M.D., Illinois.

This inquiry was referred to two consultants, whose respective replies follow.—ED.

ANSWER.—The transmission of parasites from the dog to man has been a subject for controversy for many years. There have been many reports in the literature of single incidents of infection, but in most instances the diagnosis has not been fully substantiated. Few parasites can be transmitted from the dog to man, but the conditions for their transmission are not too common. Most of the external parasites of the dog may occasionally be found on man but are only transitory. Two tapeworms of the dog may be transmitted to man, namely Dipylidium caninum and Echinococcus granulosus. The D. caninum is transmitted by infected fleas (who are the intermediate hosts of this parasite) that a human may accidentally ingest. The E. granulosus infects man as a result of the contamination of food or water with the feces of dogs. Strongyloides stercoralis is a nematode parasite that has been found in both man and dog, but whether there is direct transmission from the dog to man has not been fully determined.

ANSWER.—Dogs are not important sources of parasitism to man in the United States. Parasites transmitted directly from dogs to man may include the following species. Echinococcus granulosus, the hydatid cyst tapeworm, may utilize man as one of its intermediate hosts. The tapeworm is rare in dogs in the U. S. and hydatid disease of man is seldom reported. For prevention, avoid contamination of human food, water, and hands by canine feces. Dogs should not lick the human mouth. Children are most susceptible to such infections. Toxoplasma gondii, causing toxoplasmosis, is increasingly reported in dogs. The protozoan is apparently the same species as that reported from man. Proof of transmission from dog to man is lacking. Endamoeba histolytica, the amoebic dysentary protozoan, was recently reported in 8.4% of 143 dogs in Tennessee (Eyles and others: *J. Parasitol.* **40**:163-166, 1954). Possible transmission from dog to man is suggested via fecal contamination. Probably dogs obtain the parasite from man or from other animals. E. coli, Endolimax nana, and Pentatrichomonas hominis, human intestinal protozoans, have also been found in dogs. Ancylostoma caninum and A. braziliense are hookworms, frequently found in dogs. The larvae of A. braziliense cause a form of human dermatitis called "creeping eruption" in the southeastern states. Human infection follows contact with damp, sandy soil contaminated by dog feces. Adult dog hookworms are rarely reported in man.

Strongyloides stercoralis of man may also infect dogs. Its transmission back to man is not well understood. Ctenocephalides canis and Ct. felis are fleas commonly infecting both dogs and man. Dogs should be deflead, and contaminated households should be sprayed or dusted with chlorophenothane (DDT) or another organic insecticide. Sarcoptes scabiei var. canis causes one form of dog mange. Dermatitis occurring in man may follow the handling of mangy dogs. Dermacentor variabilis, the

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

common American dog or wood tick (and occasionally other dog-inhabiting ticks), frequently attaches to human skin. Dog ticks may be directly transferred to man, although most ticks are acquired from contact with infested grass, weeds, and bushes. Daily removal of ticks by gentle traction is recommended for man. Dogs may be bathed with tickicides. Specific instructions on the control of these parasites may be obtained from veterinarians, especially from those in small-animal practice.

Dogs may act as indirect sources of human parasitism because dogs and man share in common certain parasites that are acquired through intermediate hosts. Paragonimus kellicotti, a lung fluke, is transmitted through the ingestion of raw crayfish. Dipylidium caninum, a very common tapeworm, is transmitted to man by the accidental ingestion of dog fleas. Diphyllobothrium latum, the broad fish tapeworm, may infect man, like the dog, through the eating of raw fish, mainly northern pike and walleyes. Trichinella spiralis, the trichina worm, is fairly common in dogs. Transmission from dog to man is remote, perhaps it occurs from dog to rat, to swine, to man. Metorchis conjunctus, a biliary fluke, is rarely reported in dog and man. Raw meat from a fish, the common sucker, is the source of infection. Dioctophyma renale, the giant kidney worm, occasionally is reported in the dog and man. The infecting source is the raw meat of a fish, the bullhead. Thelazia californiensis, a so-called eye worm, is reported from dogs and rarely from man along the Pacific coast. It invades the conjunctival sacs and lacrimal ducts. The mode of transmission is unknown.

HYPOGLYCEMIA

To the Editor:—*A 40-year-old college professor who has vague abdominal and generalized complaints was studied recently at a diagnostic center, and no disease was found. The consulting psychiatrist thought the patient was under too much pressure in his work. He had done, in an excellent hospital, the modified six-hour glucose tolerance test. He awoke at 4 a. m., drank 100 gm. glucose solution flavored with lemon juice, and went back to sleep, reporting at 10 a. m. without anything else to eat or drink. His blood sugar level was 69 mg. per 100 cc. I am interested whether other workers feel that such a mild degree of hyperinsulinism could account for the symptoms usually associated with neurosis.*

M.D., Massachusetts.

Answer.—So far as is known to this consultant there has been no published confirmation of the value of the test described—100 gm. glucose at 4 a. m. with a single blood sugar determination six hours later—as proof of either organic or functional hyperinsulinism. One would hesitate to make the diagnosis on the basis of a single reading no lower than 69 mg. Of greatest value in the diagnosis of hyperinsulinism due to an islet cell tumor is the development on fasting of a blood sugar level of 50 mg. per 100 cc. or lower with no tendency to spontaneous rise. In the diagnosis of functional or neurogenic hypoglycemia, of most aid is a blood sugar value of 60 mg. or lower obtained at the time the patient's symptoms are most pronounced. In neurogenic hypoglycemia, spontaneous rise to normal may be anticipated. Along with easing of tension and the use of phenobarbital and belladonna, a diet restricted in carbohydrate and liberal in protein is useful in the treatment of neurogenic hypoglycemia.

ILLUMINATION IN TREATMENT ROOM

To the Editor:—*My treatment room has fluorescent lighting. I would like to know what type—daylight, soft white, etc.—bulbs are the best for diagnostic lighting. At times I find it difficult to detect early cyanosis or jaundice under present lighting.*

Louis P. Lapin, M.D., Bordentown, N. J.

Answer.—Color discrimination under artificial light is influenced by several factors, of which the source of illumination is probably the most important. Others are, the amount of illumination on the object viewed, the reflection from the walls and ceiling, the color of the walls and other reflecting surfaces, the color of the object to be viewed, and the ability of the viewer to discern and evaluate colors and slight color differences. Partial color blindness is a constant that may be compensated for by experience and comparative tests. Recognition of small differences in color values can be detected and appreciated by partially color blind persons, but there is a difference in the abilities of persons to achieve practical equality in discrimination. Consequently, what may be the best lighting for one person may not be so satisfactory for another. Standard illumination at the working level of the clinician in his office and clinic should average 25 foot-candles (f.c.) and for special examinations, such as of mucous membranes and dark and sallow skin, the lighting should be 30 to 50 f.-c. The reflection of light from mucous membranes is less than that from white skin. Cyanosis and jaundice in small amounts are particularly difficult to distinguish in artificial light and may be masked by too much or too little illumination. The "soft white" fluorescent tube in a neutral reflector overhead at 25 to 40 f.-c. at desk level gives the most satisfactory lighting for general clinical offices; however, there are individual differences that may make some other lighting more satisfactory for certain persons.

MICROCEPHALY

To the Editor:—*A young woman recently delivered a microcephalic infant in whom, on transillumination, an internal hydrocephalus was discovered. What are the possibilities of this woman having another similar child in future pregnancies?*

William L. Hauptmann, M.D., California.

Answer.—Microcephaly may result from maternal German measles in the first trimester of pregnancy, from therapeutic amounts of maternal pelvic irradiation, or possibly from some, as yet unknown, nonrecurring cause. It is assumed that none of these causes was operating in the case of the present family. On the basis of existing knowledge it cannot be stated with any degree of exactness what the chance is that the present mother will have another microcephalic child. This is due, in part, to the fact that no statistics are available regarding the recurrence of the condition in any large series of families, in each of which at least a microcephalic child has been born. Also, in the case of the present family, there is no information on the occurrence of microcephaly in any of the blood relatives of the affected child. The parents of a child with any malformation are more likely to have another defective offspring than would be expected by chance, and if they do so there is an unusual chance that it will be the same defect as that which affected their previous malformed child. There is reason to suspect that this latter statement applies also in the case of microcephaly, since this condition has been observed in siblings. For example, in one family of 10 children, 5 suffered from microcephaly, and in other families two and three cases have been reported. Although microcephaly has been reported in siblings, the general impression is that it is a recessive trait. There is also some evidence to indicate that microcephaly, as well as other congenital defects, increase in frequency with increasing age of the mother, particularly after 28 to 30 years of age.

PREVENTION OF BLOCKING OF INDWELLING CATHETER

To the Editor:—*Please give the formula for irrigating solution to use in an indwelling catheter in the urinary bladder to prevent blocking by deposition of crystals.*

Malcolm L. Raymond, M.D., Johnstown, Pa.

Answer.—The best method of preventing blocking by deposition of crystals on an indwelling catheter in the urinary bladder is to produce, if at all possible, an acid urine. If all other acidifying agents fail, cranberry juice might be used. Acidification of the urine is oftentimes caused by urea-splitting bacteria, and it is advisable to determine the type of bacteria present and attack this causative organism by the use of appropriate antibiotics. In order for any irrigating solution to be of considerable use in preventing the formation of crystals, a continuous irrigation would be necessary, and most solutions of this type would sooner or later become quite irritating to the bladder. Frequent changing of the urethral catheter would be the alternative for the above-mentioned methods.

RINGWORM

To the Editor:—*A family recently acquired a cat; it also had a dog. Subsequently the family developed ringworm of the body; three of the children also had a small spot or two on the scalp. The dermatologist diagnosed the children's ringworm as due to Microsporum audouini. He x-ray-epilated two of the children; this was followed by local treatment. Later animal ringworm M. canis was recovered by culture from the cat and the dog and all the lesions on the children. 1. Can the difference in the two types be told by the amount of fluorescence under Wood's light? 2. Should patients with scalp involvement caused by animal ringworm of the scalp be epilated, or should more conservative treatment be tried first? 3. Is animal ringworm of the scalp more easily cured than the usual type due to M. audouini? None of these lesions was of the kerion type. Please indicate treatment for both types of ringworm on the scalp and on the body.*

Douglas P. Arnold, M.D., Buffalo.

Answer.—1. No. 2. Conservative treatment should be tried first. 3. Yes. Apply 5% salicylanilide in a "greaseless" base daily, shampoo frequently; under Wood's light, at frequent intervals, epilate the diseased hairs with a forceps and have the youngster wear a cap constantly. If there is no progress after a reasonable period of time (two to three months), the hairs should be epilated by x-rays by somebody trained in the technique. This routine may be used for either type of ringworm of the scalp. The body types usually respond to treatment with benzoic and salicylic acid (Whitfield's) ointment diluted to one-eighth to one-fourth strength and applied several times daily.

CHEST PAIN AND TIC DOULOUREUX

To the Editor:—*A woman 59 years old weighing 140 lb. (63.5 kg.) has always had good health except some sinusitis and an attack of tic douloureux eight years ago, which was fairly well controlled for three years by injections. Finally she was operated on for the condition, with satisfactory results. Shortly after the operation she began to have pains in the left side of the chest. They were trigger pains, which became more painful, and were only relieved by intercostal nerve root injection (during the injection an accident occurred, a collapse of the left lung); the pain was relieved, however. During the past two weeks she is suffering recurrence of the chest pain with more frequency and intensity. Every classical symptom of tic douloureux is present—only the intercostal nerves on the left side, the 4th and 5th nerves as near as I can determine—are involved. It is impossible to adequately examine the area because of starting the pain. Please give information on treatment for the condition.*

J. W. Wentz, M.D., Pataskala, Ohio.

Answer.—Major neuralgia of the type that occurs in the trigeminal and glossopharyngeal nerves (trigeminal neuralgia and glossopharyngeal neuralgia) does not occur in any other nerves in the body. The intercostal neuralgia that is described here must have some other explanation. The nerve may be involved by a tumor, by a herniated intervertebral disk, by an arthritic spur, or by some other condition, such as a previous herpes zoster. Without knowing the cause for the condition in this case, it would not be possible to recommend treatment. The first indication is a thoroughgoing investigation and diagnosis.

ATROPHIC RHINITIS

To the Editor:—*What can be done for a woman over 50 years of age who has a gradual loss of sense of smell, with no antecedent disease except for a dry nose?* *M.D., Illinois.*

Answer.—A patient over the age of 50 who has had a dry nose is probably suffering from atrophic rhinitis. This condition is characterized by an atrophy of the mucous membrane of the nose, including the mucus-producing glands. The symptoms vary from a mildly dry nose to a severe crusting and foul-smelling condition. There is an associated atrophy of the olfactory mucosa including the glands of Bowman, which produce a secretion into which the odoriferous particles are normally imbedded in the process of olfaction. There is no known curative treatment for atrophic rhinitis or the associated anosmia. For the common nasal preparations used for symptomatic relief of atrophic rhinitis the reader may refer to any of the common textbooks of otolaryngology.

BISMUTH SUBNITRATE

To the Editor:—*Is there any clinical evidence that bismuth subnitrate in ointment form applied topically to the skin is absorbed through the intact skin and might cause nitrous oxide poisoning?* *M.D., Pennsylvania.*

Answer.—No; nor is such a reaction likely to occur because the subnitrate radical, if it converts, would probably convert in the direction of a nitrite. Nitrite poisoning has been reported from high doses of bismuth nitrate administered orally—doses of 30 to 60 gm. within a 24 hour period; it is inconceivable that such an amount could be absorbed from an ointment.

DEATHS FROM ANTIBIOTICS

To the Editor:—*In an inquiry on "Differentiation Between Viral and Bacterial Respiratory Infection" in* The Journal *on May 21, 1955, page 239, one question raised was: "What is the actual number of deaths reported as directly or indirectly attributable to antibiotics in general and to penicillin in particular?" I would like to comment on this question. A recent search of the literature revealed a total of 48 anaphylactic deaths reported from penicillin and 34 deaths from aplastic anemia following chloramphenicol administration (Hussar, A. E., and Holley, H. L.: Antibiotics and Antibiotic Therapy, New York, the Macmillan Company, 1954). Fatalities reported from micrococcic (staphylococcic) enteritis, fungal or other superinfections, periarteritis nodosa, renal toxicity, intrathecal administration, and other causes have not been counted but may be roughly estimated at about 100 cases. These figures, however, do not represent the true incidence of fatal antibiotic reactions, since a considerable number of cases remain unreported. I know of at least six antibiotic fatalities that were never reported. Certainly, many other physicians have similar knowledge. It is a fair estimate then, that probably several hundred persons have died from antibiotic administration. True, this incidence is a very small percentage of the total number who have received antibiotics. However, it would be erroneous to minimize the charge of promiscuity in the use of a therapeutic agent solely because of the low percentage of fatal reactions. No matter how small the statistical figures, they became 100% for those physicians who lost their own children through such accidents. When dealing with human lives, even small risks have to be taken with great caution and, therefore, the risk of antibiotic administration must be well balanced by a justifiable indication for such medication. Peculiarly enough, accidents often hit when unjustified risks are taken. An analysis that I have made of the reported fatalities has revealed that about one-half of these individuals died from unnecessary antibiotic medication.*

The indiscriminate use of antibiotics should be condemned not only because of untoward drug reactions, but also for many other reasons, among which two should weigh heavily: the threat to the future usefulness of present-day antibiotics and the threat to our professional standards.

Allen E. Hussar, M.D.
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CANKER SORES

To the Editor:—*I have read with great interest the various letters in Queries and Minor Notes dealing with treatment of canker sores. About a year ago I was privileged to try a new germicide called Clorpactin WCS-90, which is a brand of monoxychlorosene. I have had success in treating 19 cases of canker sores locally with this powerful and apparently nontoxic germicide. A paper on my experiences and results with Clorpactin WCS-90 will be published in the August, 1955, issue of the* A. M. A. Archives of Otolaryngology.

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